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CARDIAC OUTPUT AND BLOOD VOLUME IN CHRONIC COR PULMONALE*

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THE CARDIAC output in chronic cor pulmonale due to advanced diffuse obstructive emphysema has been the subject of a number of investigations. Richards[1] found the cardiac output to be normal in six patients in right heart failure due to chronic cor pulmonale of unstated cause. Harvey *et al.*[2] could demonstrate no abnormality in the resting cardiac output in patients with mild emphysema. In those with severe emphysema, with or without a history of right heart failure, there was a slight elevation of cardiac output. The patients with frank but reversible right heart failure had a high cardiac output. Two patients with irreversible right heart failure had a lower cardiac output than those who subsequently recovered. Dexter[3] was not able to demonstrate a high cardiac output in any of 18 patients with pulmonary diseases, which included kyphoscoliosis, pulmonary fibrosis, chronic bronchitis, asthma and emphysema. In about half the patients the right ventricular diastolic pressure was high, but in none was right heart failure an outstanding feature. Lewis *et al.*[4] showed the average resting cardiac output to be within the normal range in chronic lung disease with or without right heart failure. Fowler *et al.*[5] showed that the cardiac output was normal in eight patients and low in four patients with chronic cor pulmonale. Mounsey *et al.*[6] and Whitaker[7] reported the cardiac output in patients with emphysema to be similar irrespective of the presence of or absence of cardiac failure.

There is general agreement that in those patients with chronic cor pulmonale who have a high total blood volume, the increase is almost entirely due to a raised red cell volume.[1, 2, 8]

In the present investigation cardiac output and blood volume were measured in 69 patients with pulmonary disease. The clinical groups were kyphoscoliosis, pulmonary fibrosis with emphysema, emphysema without the history of right heart failure, emphysema recovered from right heart failure and emphysema in frank right heart failure. The patients with emphysema were further subdivided into those with and those without significant pulmonary fibrosis. A group of six patients with polycythemia rubra vera has been included for comparison.

MATERIAL

The number of patients in each group with details of sex and age are shown in Table I. The diagnosis in each case was based on clinical and roentgenographic examination and respiratory function tests. Pulmonary function tests were performed on all cases except five that were severely ill with right heart failure. The criteria for the diagnoses of pulmonary fibrosis, emphysema and emphysema with pulmonary fibrosis have been previously described.[9] The diagnosis of right heart failure was made when the physical signs of increased jugular venous pressure, hepatomegaly or peripheral edema were present. Patients in whom an obvious cause for cardiac failure was apparent, other than chronic cor pulmonale, were excluded from the investigation. Cardiac output and blood volumes were measured in 73 control subjects comprising normal hospital staff and hospital patients without evidence of heart or lung disease.

METHODS

In addition to clinical examination, roentgenograms and electrocardiograms were taken. The respiratory function tests performed were the forced vital capacity recorded on a Collins 9-litre spirometer and the maximum breathing capacity using a low-resistance valve and Douglas bag. Oximetry was used to measure the 90% desaturation time, a test for emphysema,[9, 10] and to record the change in the arterial oxygen saturation during a one-minute 30-step exercise test.[10] In some cases lung volumes were measured by a closed-circuit helium method. The cardiac output was calculated

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TABLE I.—DIAGNOSIS, AGE AND SEX

Diagnosis	*Number of patients*	*Male*	*Female*	*Mean age*	*Range of age*
Polycythemia vera	6	4	2	59	37 - 72
Kyphoscoliosis	9 (3)*	4	5	43	17 - 75
Pulmonary fibrosis	10 (2)*	10	0	47	31 - 64
Emphysema:					
No RHF	22 (8)	22	0	53	27 - 65
Previous RHF	16 (5)	15	1	52	37 - 68
In RHF	12 (5)	12	0	64	40 - 79
Total	75	67	8		
Controls	73	72	1	41	15 - 74

RHF = Right heart failure.
( )* = Number of patients in right heart failure or with past right heart failure.
( ) = Number of patients with significant pulmonary fibrosis in addition to emphysema.

from an Evans blue (T-1824) dye dilution curve, recorded by a direct writing ear oximeter.[11, 12] The central blood volume was calculated from the Newman formula.[13] Plasma volume was obtained from the plasma dye dilution, the red cell volume and the total blood volume from the uncorrected hematocrit.

RESULTS

The cardiac output and blood volume results are shown in Table II and in Figs. 1 and 2. Cardiac output was normal in five of the six patients with polycythemia rubra vera. Cardiac output was normal or low in eight of the nine patients with kyphoscoliosis, two of whom had been in right heart failure. The cardiac index was high in one patient (Fig. 1). This woman was in right heart failure and had a cardiac output of five litres per minute. The high cardiac index was possibly due to the very small body surface area of 1.06 m.^{2} Cardiac output was normal in 9 of 10 patients with diffuse pulmonary fibrosis, two of whom had been in right heart failure. The cardiac output was high in one patient; he had an alveolar capillary block and was a particularly apprehensive individual.

Cardiac output was normal or low in 48 of the 50 patients with emphysema. The cardiac ouput was high in two patients both of whom had been in right heart failure. The mean cardiac output was significantly lower in the group in right heart failure when compared with the other two emphysema groups, namely those who had never had heart failure and those who had been in heart failure in the past (t test = $p < 0.01$). Cardiac output was low in eight of the 12 patients with emphysema in right heart failure. There were no significant differences in cardiac output in those patients with emphysema alone and in those with emphysema and additional diffuse pulmonary fibrosis.

Central blood volumes were similar in all groups.

Red cell volume was high in the patients with polycythemia rubra vera (Fig. 2). The mean red cell volumes of the patients with kyphoscoliosis and pulmonary fibrosis were not significantly different from that of the normal subjects. Red cell volume was normal or low in the three patients with kyphoscoliosis with past or present right heart failure. The red cell volume was high in the two patients with diffuse pulmonary fibrosis who had been in right heart failure. The mean red cell volume was significantly higher in the emphysema groups with present or past right heart failure when compared with the group in whom there had never been right heart failure (t test = $p < 0.01$).

Plasma volume was normal in all groups and the total blood volume was high only in those groups with a high red cell volume.

The results of the respiratory function tests are shown in Table III. The tests helped to separate the groups and excluded the presence of significant pulmonary disease in patients wih polycythemia rubra vera. There was little difference in pulmon-

TABLE II.—CARDIAC OUTPUT AND BLOOD VOLUME DATA IN CONTROL SUBJECTS AND IN PATIENTS WITH PULMONARY DISEASE AND POLYCYTHEMIA VERA

Diagnosis	*Number of patients*	*C.I.* Mean ± SD	*C.V.I.* Mean ± SD	*Hct.* Mean ± SD	*T.B.V.* Mean ± SD	*R.C.V.* Mean ± SD	*P.V.* Mean ± SD
Polycythemia vera	6	3.9 ± 0.9	524 ± 180	60.8 ± 10.2	110.0 ± 10.4	66.8 ± 12.7	43.2 ± 11.9
Kyphoscoliosis	9	3.1 ± 0.9	556 ± 322	41.8 ± 5.5	80.3 ± 11.2	33.6 ± 6.8	46.7 ± 7.2
Pulmonary fibrosis	10	3.6 ± 0.8	607 ± 150	47.7 ± 8.3	87.1 ± 9.8	41.8 ± 9.9	45.3 ± 7.7
Emphysema:							
No RHF	22	3.2 ± 0.6	506 ± 144	48.8 ± 6.5	84.2 ± 13.0	41.1 ± 9.1	43.1 ± 8.3
Previous RHF	16	3.6 ± 0.8	675 ± 225	56.7 ± 18.6	104.6 ± 23.0	59.9 ± 19.3	44.7 ± 12.7
In RHF	12	2.6 ± 0.9	534 ± 108	53.2 ± 5.3	102.0 ± 21.0	54.9 ± 15.0	47.1 ± 7.6
Controls	73	3.5 ± 0.9	557 ± 171	42.7 ± 5.1	80.7 ± 14.3	34.3 ± 7.6	46.4 ± 9.2

C.I. = Cardiac index (litres/min./M^2 body surface area).
C.V.I. = Central volume index (ml./M^2 body surface area).
Hct. = Hematocrit (%).
T.B.V. = Total blood volume (ml./kg.).
R.C.V. = Red cell volume (ml./kg.).
P.V. = Plasma volume (ml./kg.).
S.D. = Standard deviation.

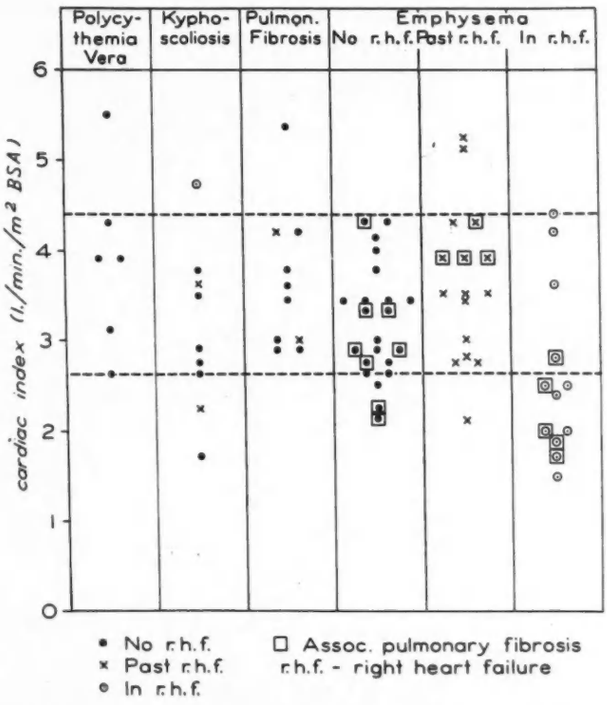

Fig. 1.—Cardiac index in patients with pulmonary disease and patients with polycythemia vera. The dotted lines show ± SD about the means of the control group.

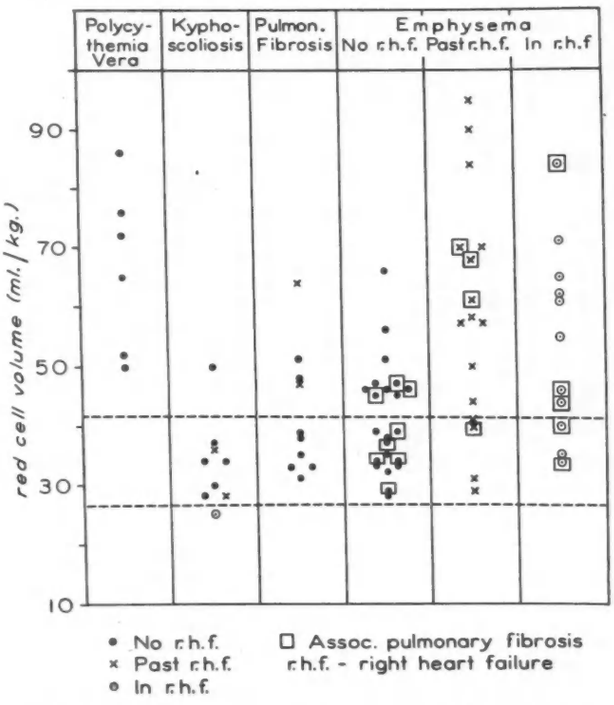

Fig. 2.—Red cell volume in patients with pulmonary disease and patients with polycythemia vera. The dotted lines show ± SD about the means of the control group.

ary function between the emphysema groups, but it was impossible to test the five most severely ill patients who were in right heart failure.

Discussion

The present investigation has shown that most patients with emphysema who are also in right heart failure have a low cardiac output like other types of cardiac failure. In some cases the output may remain within normal limits. A high cardiac output in patients with emphysema, with or without right heart failure and with or without associated pulmonary fibrosis, is very unusual. No relationship could be shown between cardiac output and the fall of arterial oxygen saturation on standard exercise. There was also no relationship between cardiac output and maximum breathing capacity, or between cardiac output and the 90% desaturation time, which is a measure of ventilation-perfusion relationships.

It has been confirmed that right heart failure due to chronic pulmonary disease is associated with hypervolemia due to an increase in red cell volume. This occurred not only in patients with frank right heart failure, but also in those recovered from right heart failure. Exceptions were the three kyphoscoliotic patients in right heart failure or with past right heart failure, who had normal or low red cell volumes. Patients in congestive failure due to heart disease, other than pulmonary disease, have high blood volumes, but the red cells and plasma are both increased.[15]

It has been suggested that the high cardiac output reported in chronic pulmonary disease might be partly due to hypervolemia.[8] Statistical analysis of the patients with emphysema shows that an

TABLE III.—Results of Respiratory Function Tests in Patients with Pulmonary Disease and Polycythemia Vera

	F.V.C.	*M.B.C.*	*90% desaturation*	*A.O.S. Ex.*
	Mean ± S.D.	*Mean ± S.D.*	*Mean ± S.D.*	*Mean ± S.D.*
Polycythemia vera	109.0 ± 21.6	111.1 ± 16.5	234 ± 46	1.1 ± 0.9
Kyphoscoliosis	45.8 ± 30.5	54.2 ± 26.6	243 ± 75	7.6 ± 7.5
Pulmonary fibrosis	71.0 ± 16.9	67.3 ± 24.6	288 ± 33	6.0 ± 5.1
Emphysema:				
No R.H.F.	64.8 ± 14.9	34.9 ± 18.9	523 ± 151	8.1 ± 5.3
Previous R.H.F.	58.5 ± 10.9	31.1 ± 8.3	646 ± 185	7.5 ± 5.0
In R.H.F.	52.6 ± 16.2	34.9 ± 17.5	613 ± 150	7.4 ± 4.0

R.H.F. = right heart failure.
F.V.C. = forced vital capacity as percentage of normal.[14]
M.B.C. = maximum breathing capacity as percentage of normal.[14]
90% Desat. = 90% desaturation time (seconds). Normal less than 350 sec.[9]
A.O.S. Ex. = fall of arterial oxygen saturation on exercise in % saturation, normal less than 3.8%.[10]
S.D. = Standard deviation.

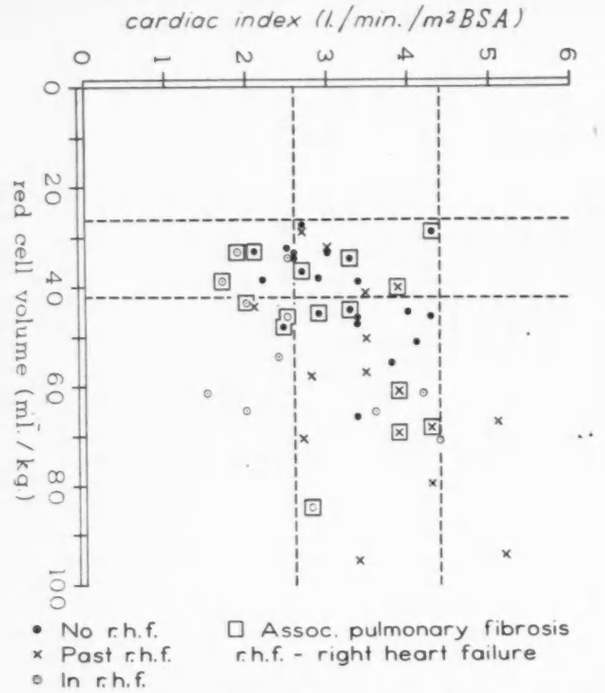

Fig. 3.—Cardiac index related to red cell volume in 50 patients with emphysema. The dotted lines show ± SD about the means of the control group.

increase in cardiac index occurs with increasing red cell volume ($r = 0.426$, $p < 0.01$). Further examination shows that this correlation occurs only in those patients with emphysema who do not have significant additional pulmonary fibrosis. In part, this may be due to inability of patients with additional pulmonary fibrosis to increase cardiac output because of a greater amount of irreversible obstruction in the pulmonary capillary bed. The wide scatter of the results is shown in Fig. 3, and despite increased blood volume most patients had a normal or low cardiac output. Further support of the view that hypervolemia *per se* does not usually cause a high cardiac output was furnished by normal cardiac output values in polycythemia rubra vera.

In those patients with emphysema and right heart failure who maintain a normal cardiac output, factors other than hypervolemia probably play a role. It has been suggested by Mack and Snider[8] that activity of infection in the lung, which is nearly always present, tends to increase oxygen consumption and leads to an increase in cardiac output even in the absence of fever. Increased work of breathing and chronic anoxia also dispose to increased cardiac output. These factors that tend to increase the cardiac output in patients with emphysema were not, however, sufficient to raise it above normal levels in the present series.

It has been suggested that hypervolemia results in an increased residual volume of blood in the lungs in patients with severe emphysema, and that this contributes to right heart failure by causing a rise in pulmonary artery pressure.[8] Although the technique used in the present investigation for the estimation of central blood volume may not be an exact measure of the blood contained in the lungs, the results do not confirm this theory. A high blood volume as such need not mean a high volume of blood in the lungs, as is shown by the normal values in patients with polycythemia rubra vera, and in those with emphysema with past or present right heart failure.

Why is the red cell volume increased in some patients with emphysema? This might be due to stimulation of the bone marrow by chronic anoxia, but many patients are not polycythemic in spite of marked arterial oxygen desaturation.[8, 16] In the present series, no measurements of the arterial oxygen saturation at rest, by the Van Slyke technique, were available, but no relationship could be shown between red cell volume and the fall of arterial oxygen saturation on standard exercise. There was no relationship between red cell volume and maximum breathing capacity, or between red cell volume and the 90% desaturation time. The factors relating to the increase in red cell volume are not apparent from the present investigation.

It was surprising that there was no evidence of more severe pulmonary dysfunction in those patients with past or present right heart failure compared with those with emphysema alone. Pulmonary hypertension is the principal mechanical cause of right heart failure in emphysema, and the pulmonary function studies done probably do not provide an index of pulmonary artery pressure. Dexter[3] found no correlation between maximum breathing capacity, vital capacity and residual volume and pulmonary arteriolar resistance.

A comparsion was made between the cardiac output and blood volume data of those patients who were in right heart failure and died, and those who recovered. There was little difference between the results of these two groups, and the observation of Harvey[2] that the patients with low cardiac output were the ones more likely to die was not confirmed.

It seemed of interest to determine how often electrocardiographic signs of right ventricular preponderance and right auricular hypertrophy were present in the different emphysema groups. These electrocardiographic abnormalities were present in only 7 of 19 patients who had never had right heart failure. The changes were present in the majority of patients (22 of 28) with present or past right heart failure.

Twelve of the patients with emphysema who had no history of right heart failure at the time of the original tests were followed up for periods from 18 months to five years. Seven developed right heart failure, and of these five had had a hematocrit of over 50% and four had had an abnormal electrocardiogram at the time of the original tests. From a prognostic point of view, the type of patient with emphysema who seems likely to develop right heart failure is plethoric, has a hematocrit of over 50% and has signs of right ventricular preponderance or right auricular hypertrophy on the electrocardiogram.

SUMMARY

Cardiac output and blood volumes were measured in 50 patients with emphysema. Twelve had frank right heart failure, 16 had recovered from right heart failure and 22 had never had right heart failure. These measurements were compared with those of six patients with polycythemia rubra vera, 10 patients with diffuse pulmonary fibrosis, nine patients with kyphoscoliosis and 73 normal subjects. Cardiac output and central blood volume were determined from an ear oximeter Evans blue dye curve. Blood volumes were calculated from the plasma dye dilution and hematocrit.

Patients with emphysema or pulmonary fibrosis who developed right heart failure usually had a high blood volume due to a raised red cell volume. Right heart failure was not associated with a raised red cell volume in three patients with kyphoscoliosis. Hypervolemia due to either primary or secondary polycythemia did not cause a raised cardiac output nor an increased volume of blood in the lungs.

Patients with emphysema in right heart failure did not have a raised cardiac output, but usually have a low cardiac output, like other types of cardiac failure.

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REFERENCES

1. RICHARDS, D. W., JR.: *Fed. Proc.*, **4**: 215, 1945.
2. HARVEY, R. M. *et al.*: *Am. J. Med.*, **10**: 719, 1951.
3. DEXTER, L.: *Bull. New England M. Center*, **11**: 240, 1949.
4. LEWIS, C. S. *et al.*: *Circulation*, **6**: 874, 1952.
5. FOWLER, N. O., JR. *et al.*: *Ibid.*, **6**: 888, 1952.
6. MOUNSEY, J. *et al.*: *Brit. Heart J.*, **14**: 153, 1952.
7. WHITAKER, W.: *Quart. J. Med.*, **23**: 57, 1954.
8. MACK, I. AND SNIDER, G. L.: *Circulation*, **13**: 419, 1956.
9. WOOLF, C. R.: *Am. Rev. Resp. Dis.*, **80**: 705, 1959.
10. WOOLF, C. R., GUNTON, R. W. AND PAUL, W.: *Am. Rev. Tuberc.*, **74**: 511, 1956.
11. BEARD, E. F., NICHOLSON, J. W., III AND WOOD, E. H.: *J. Lab. & Clin. Med.*, **36**: 798, 1950 (abstract).
12. GUNTON, R. W. *et al.*: In preparation.
13. NEWMAN, E. V. *et al.*: *Circulation*, **4**: 735, 1951.
14. BALDWIN, E. DE F., COURNAND, A. AND RICHARDS, D. W., JR.: *Medicine*, **27**: 243, 1948.
15. GUNTON, R. W. AND PAUL, W.: *J. Clin. Invest.*, **34**: 879, 1955.
16. WILSON, R. H., BORDEN, C. W. AND EBERT, R. V.: *Arch. Int. Med.*, **88**: 581, 1951.

STUDIES ON THE FINE STRUCTURE OF PROLIFERATED BILE DUCTULES:

II. CHANGES OF THE DUCTULE–CONNECTIVE TISSUE ENVELOPE RELATIONSHIP*

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IN THE first paper of this series we have described some of the differences between the ultrastructural morphology of normal and proliferated biliary epithelial cells.[1]

The "ductular cell reaction" has been defined as a non-specific response of the liver to injury. It consists of a proliferation of bile ductular cells and of inflammatory and other mesenchymal cells in and around portal tracts.[3] Some of the cells previously designated as undifferentiated "oval" cells have been identified in the electron microscope as small bile ductules.[2] In addition to these changes connective tissue cells proliferate around ductules and new extracellular fibres are laid down. This process has been studied with the electron microscope in a large variety of human diseases and in subacute ethionine intoxication and after intrahepatic carrageenin injections in rats.[4] This change has been designated as periductular fibrosis.

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It is the purpose of this paper to examine the relationship of connective tissue fibrils to proliferated ductules. Attention will be also paid to some aspects of the periductular and intraductular proliferation and infiltration of inflammatory cells.

MATERIALS AND METHODS

The animals as well as the light and electron microscopic methods employed are identical with those used for the preparation of the previous paper in this series.[1]

PRELIMINARY CONSIDERATIONS

The Fine Structure of Normal Terminal Pathways of Bile Conduction

Diagram I depicts a three-dimensional reconstruction of bile canaliculi, bile preductules and bile ductules. The sinusoid (s) of the liver lobule is bounded by a Kupffer cell (K) which is separated from parenchymal liver cells (plc) by the perisinusoidal space of Disse (ps). Bile canaliculi (bc) which do not communicate with sinusoids are channels which possess no specialized lining. They are formed by a separation of adjacent parenchymal liver cells which are provided with microvilli on the surface facing the canalicular lumen. Bile preductules (ducts of Hering) (pd) are continuous with canaliculi. They are lined by biliary epithelial cells which are surrounded by a basement membrane (bm). The basement membrane forms a covering for all biliary pathways beyond canaliculi. It is only interrupted at the

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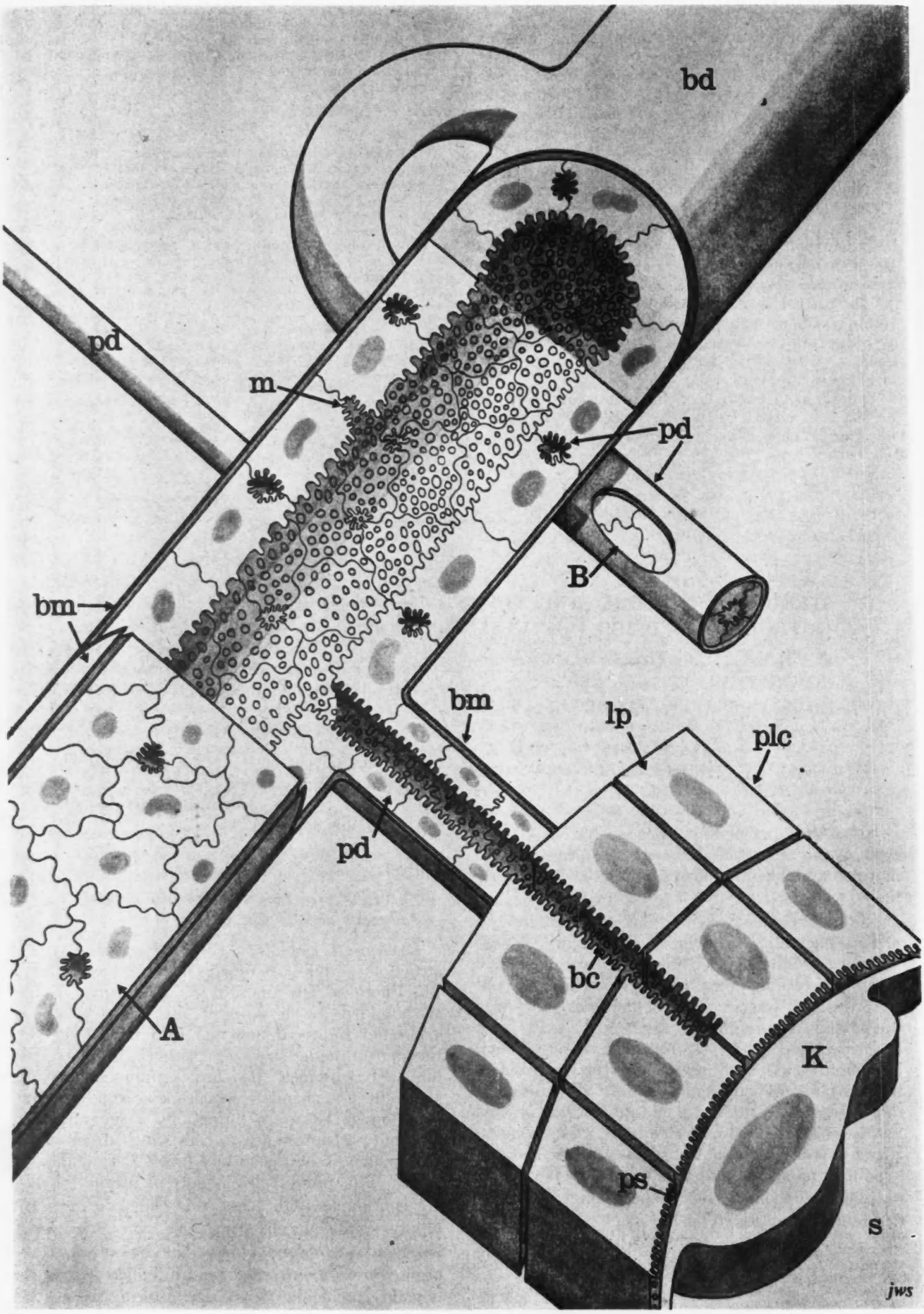

Diagram 1.—For legend, see text.

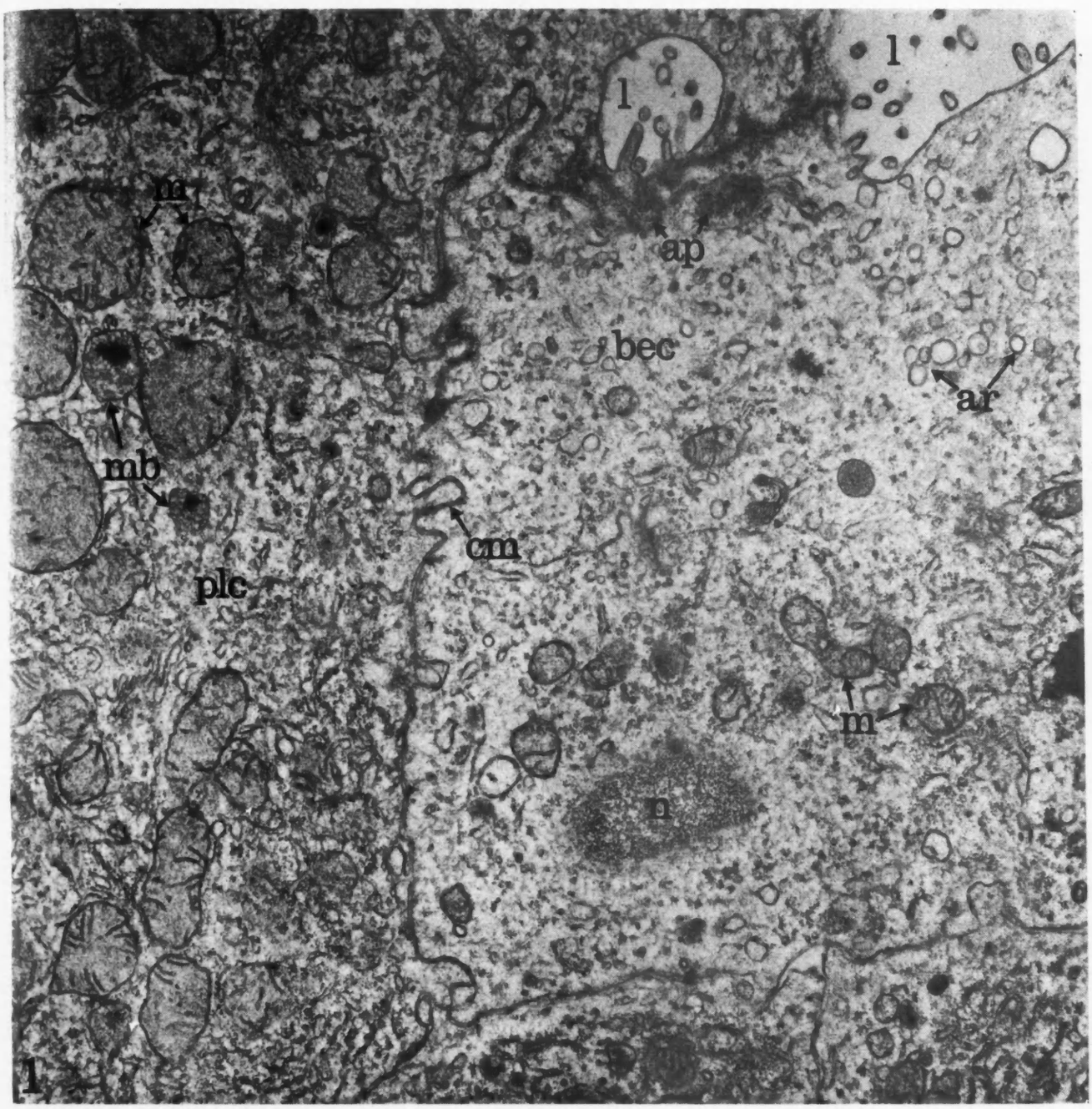

Fig. 1.—Point of contact between a parenchymal liver cell and a biliary epithelial cell. They can be differentiated because of the distinct appearance of their mitochondria, even at relatively low magnification. Note that the cells interlock to some extent. Such areas of contact are seen more frequently in the ductular cell reaction than normally. Note also the relative concentration of organelles in the two cells. The nucleus of the biliary epithelial cell is sectioned tangentially. Uranyl acetate stain, × 17,600.

KEY TO ABBREVIATIONS FOR FIGS. 1 TO 14.

ap — attachment plate
ar — agranular reticulum
bd — bile ductule
bec — biliary epithelial cell
bm — basement membrane
cm — cell membrane
d — desmosome
f — fibroblast
fib — connective tissue fibrils
ic — intercalated biliary epithelial cell
l — lumen of biliary channel
lip — lipid inclusion body
ly — lymphocyte
m — mitochondrion
mb — microbody
me — mesenchymal cell
mv — microvilli
n — nucleus
ncl — nucleolus
pd — bile preductule (duct of Hering)
plc — parenchymal liver cell
pol — polymorphonuclear leukocyte (neutrophil)

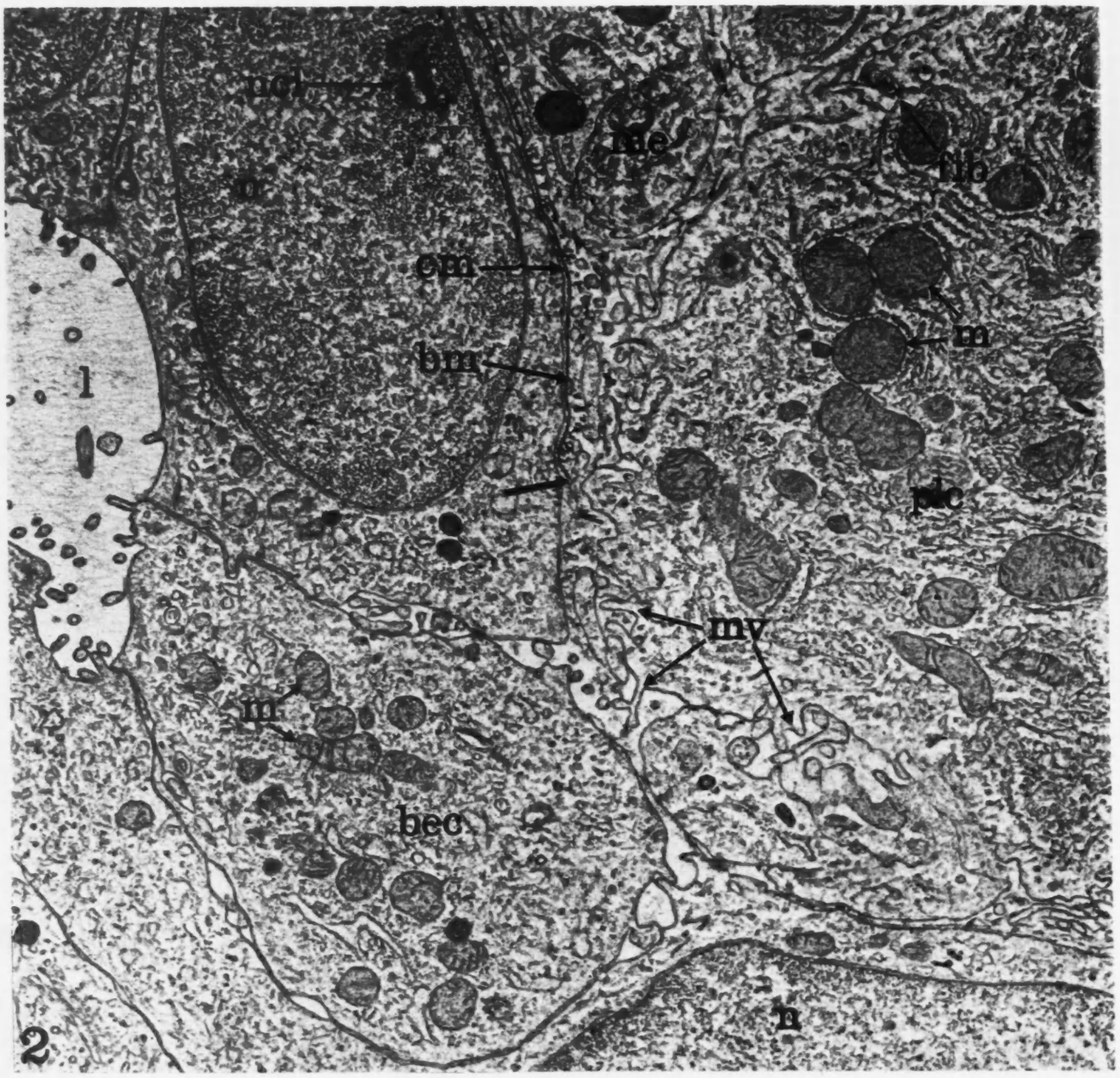

Fig. 2.—The lumen of a proliferated bile ductule is present at the left margin of the picture. The biliary epithelial cell containing a nucleus is separated from an adjacent mesenchymal cell (probably a lipid-containing macrophage) by a basement membrane and a few cross-sectioned connective tissue fibrils. The basement membrane stops abruptly at the point marked with an unlabelled arrow. Beyond this a parenchymal liver cell, provided with microvilli, is in contact, though not interlocking with a biliary epithelial cell. The intervening space communicates with the connective tissue surrounding the ductule. Note the difference in appearance of mitochondria of biliary epithelial cells and of the liver cell. Phosphotungstic acid stain, × 15,200.

point where the marginal liver plate (lp) of the lobule is in contact with biliary epithelial cells of the preductule. In a transverse two-dimensional section the preductule is formed by a focal separation of two adjacent biliary epithelial cells. It enters the lumen of a ductule through a mouth (m). The bile ductule (bd) is formed by a rosette of biliary epithelial cells, entire cell surfaces of which face the lumen. When a section through a ductule or preductule misses the lumen a group of interlocking epithelial cells bounded by a basement membrane can be observed (A and B).

The Normal Connective Tissue Envelope of Ductules

The basal portion of biliary epithelial cells is surrounded by a clear zone which separates it from a *basement membrane*.[5] The basement membrane is a single layer of electron-dense material devoid of periodicity.[4] We have noted that branching is seen fairly commonly in human material.[6] Since this structure stains extremely intensely with the periodic-acid–silver-methenamine stain, it was suggested that it may be composed of glycoprotein.[6] The origin of the basement membrane is

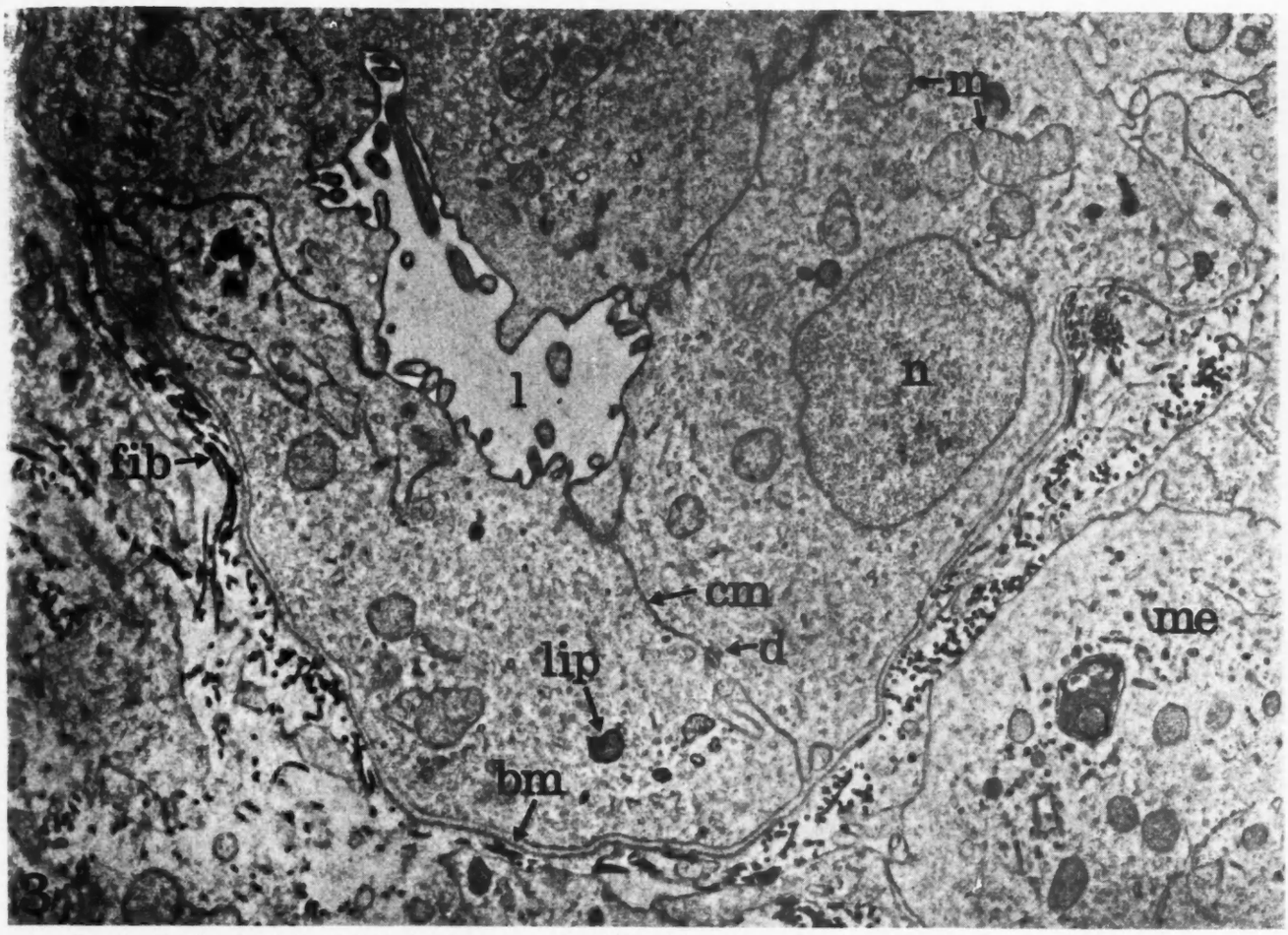

Fig. 3.—Proliferated bile ductule showing a normal relationship to its connective tissue envelope. The basement membrane is at times indistinct owing to tangential sectioning. The concentration of connective tissue fibrils is in no way different from the amount demonstrable around normal ductules at a comparable magnification. Note that this stain accentuates the luminal lining, the connective tissue fibrils and lipid bodies within cells. Phosphotungstic acid, × 15,900.

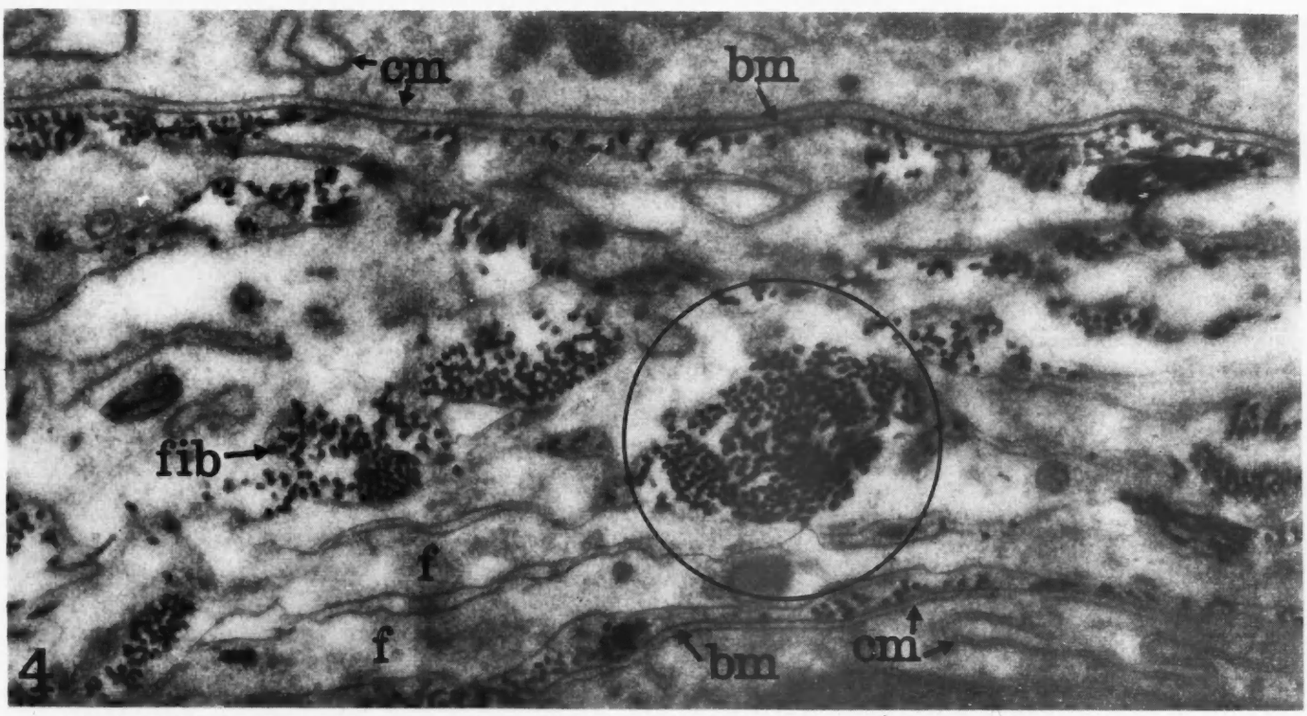

Fig. 4.—The connective tissue envelope of two adjacent proliferated ductules, each of which is separated from it by a basement membrane. Fibroblastic processes lie between variable-sized bundles of fibrils. The encircled area may correspond to a fibre visible as a distinct entity at a light microscopic level of observation. Note that most fibrils are seen in cross-section suggesting that they are aligned in parallel to the long axis of ductules. Phosphotungstic acid stain, × 23,310.

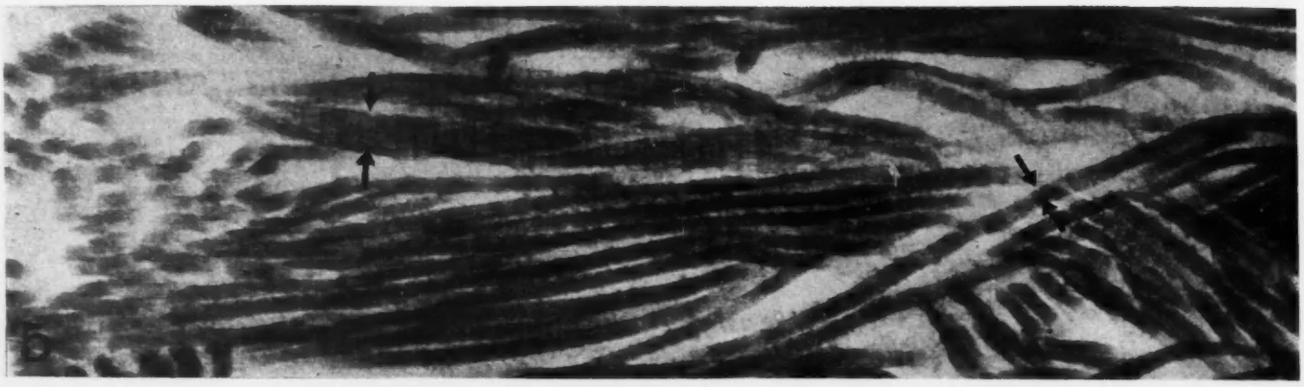

Fig. 5.—Two types of fibrils identified in the periductular connective tissue. The wider of the two probably represents collagen fibrils and the narrower reticulin. Their periodicity is identical. Phosphotungstic acid stain. × 59,200.

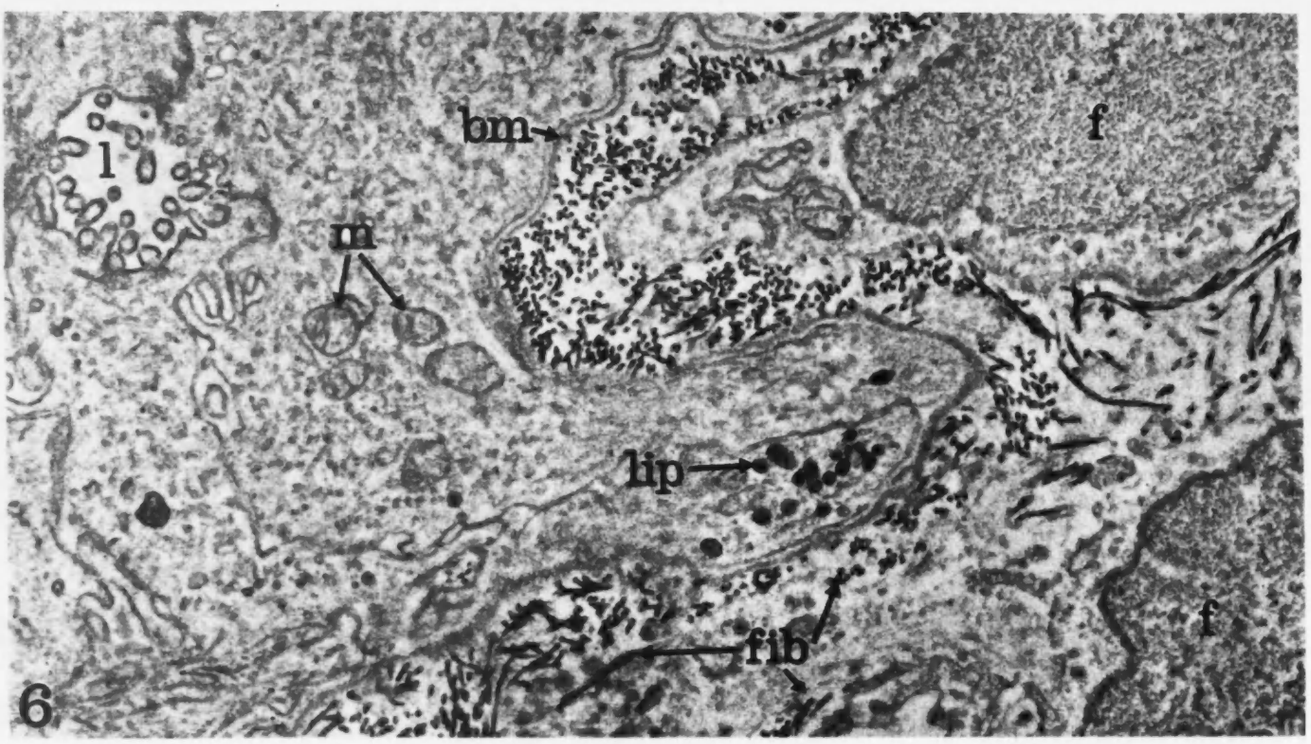

Fig. 6.—The rather irregular outline of a ductule is caused by a spur projecting from its surface. This probably represents a point of branching or is an expression of tortuosity of the proliferated channels. Note the fibroblast with its adjacent connective tissue fibrils projecting into the recess formed by the spur. Phosphotungstic acid. × 18,300.

unknown. It is not clear whether the basement membrane is elaborated by biliary epithelial cells or by fibroblasts in the connective tissue. The basement membrane abuts on to all cells which constitute the lining of ductules and preductules and is only lacking at the points of direct contact between biliary epithelial cells and parenchymal liver cells.[2, 6]

Beyond the basement membrane lie *collagen fibres*[5] which are applied to and insert into the basement membrane.[2]

RESULTS

The observations made in rabbits and rats after ligation of the common bile duct (Experiment I) and in rats after prolonged administration of carbon tetrachloride (Experiment II) were essentially identical. They will be described together.

Connections Between Biliary Epithelial Cells and Liver Cell Plates

We have stated previously that the points of contact between parenchymal liver cells and biliary epithelial cells, where bile canaliculi enter the confines of the latter cells lining preductules, are seen only rarely in normal tissue.[6] When bile ductules proliferate these points of contact are seen frequently (Figs. 1 and 2). Where biliary epithelial cells directly adjoin parenchymal liver cells, they interlock by means of processes and indentations, though these are less numerous than between adjacent biliary epithelial cells (Fig. 1). The basement membrane usually reaches to the very point where contact between the two cell types has been established (Fig. 2). Occasionally, however, an angular gap remains and here paren-

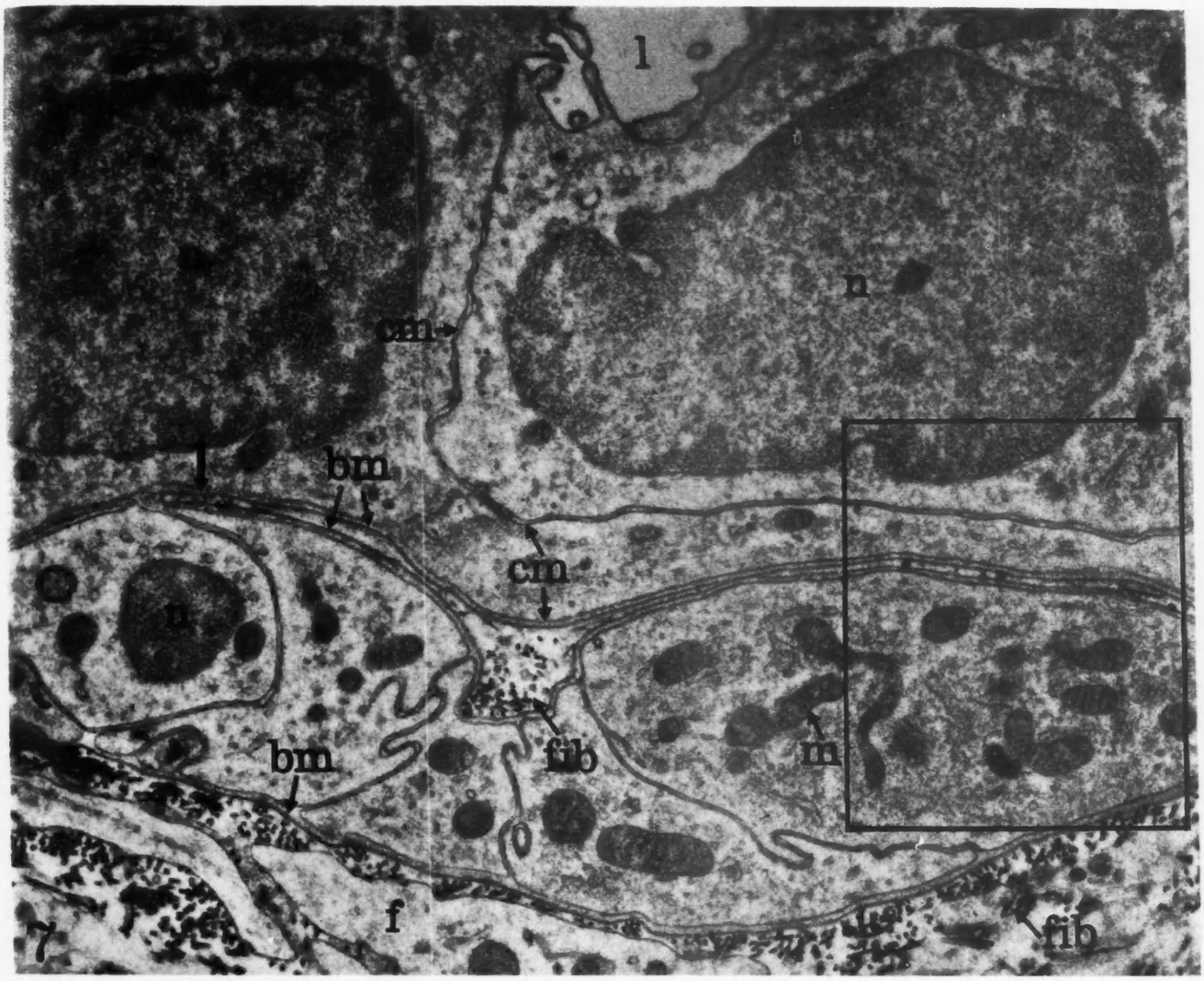

Fig. 7.—A proliferated ductule is seen in the upper half of the micrograph. The lower half is occupied by a ribbon of approximately five biliary epithelial cells. A basement membrane surrounds either side of this group of cells and another limits the inferior border of the ductule. This represents a ductule and a ductular spur. Connective tissue fibrils are enclosed in a pocket between the two adjacent basement membranes (unlabelled arrow and arrow labelled "fib"). The area enclosed in a square is seen at higher magnification in Fig. 8. Phosphotungstic acid, × 16,280.

chymal liver cells lie some distance from the biliary epithelial cells, separated by connective tissue (Fig. 2). It is at times difficult to establish the exact point at which the basement membrane ends, as its extremity appears somewhat frayed.

Disturbances of the Relationship Between Biliary Epithelial Cells and their Connective Tissue Envelope

In most proliferated bile ductules and preductules the relationship between the lining cells, their basement membrane and the surrounding connective tissue cells and extracellular fibrils remains undisturbed (Figs. 3, 4 and 5). Owing to the marked branching and tortuosity of the proliferated penultimate channels of bile conduction, sections often pass through surface areas of the branches creating the picture of *ductular spurs and knuckles* projecting from the surface of the bile ductules (Figs. 6 and 7). These may maintain their connection with the mass of biliary epithelial cells surrounding the lumen (Fig. 6). Occasionally the spurs are cross-sectioned and they lie as separate basement-membrane-enclosed cell groups adjacent to a neighbouring ductule (Fig. 7). In this way a spur and its parent ductule may come to lie in close apposition, their basement membranes nearly in contact with each other except for the presence of occasional collagen fibrils in the intervening space (Fig. 8).

Indentations and branching of the basement membrane are seen occasionally. A narrow ribbon-like band of connective tissue fibrils surrounds most of the ductules. Such fibrils are usually seen in cross-section since their course parallels that of the long axis of the ductule (Fig. 4). Where indentations of the basement membrane occur, such juxtamembranous fibrils find themselves within a pouch formed by the tortuous basement membrane (Figs. 9 and 10). At times fibrils were seen between epithelial cells a short distance away from the

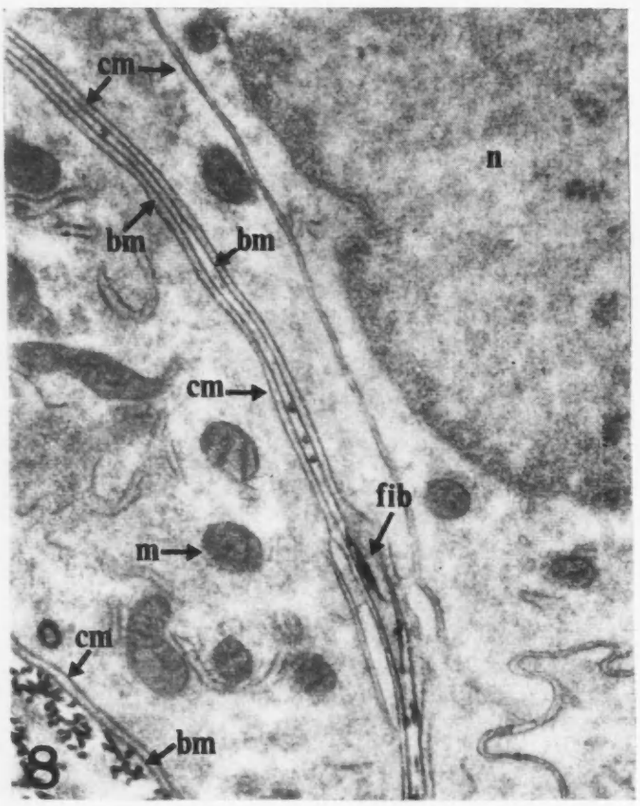

Fig. 8.—Connective tissue fibrils enclosed in a narrow pocket between two adjacent basement membranes of biliary epithelial cells. Phosphotungstic acid, × 19,240.

basement membrane, apparently lacking the basement membrane covering. This observation has been made only rarely. Intracytoplasmic connective tissue fibrils were never observed.

Evidence of Ductular Inflammation

All components of an inflammatory reaction could not be demonstrated in the connective tissue surrounding proliferated bile ductules. In well-preserved tissue the various mesenchymal cells and the extracellular fibrils fit closely together, often in an interlocking fashion. In some areas where they are slightly separated from each other a faintly electron-opaque material is present which we interpret as ground substance. We were unable to recognize the presence of edema fluid in well-preserved tissue.

Apart from fibroblasts and macrophages, the most prominent cells were polymorphonuclear leukocytes (neutrophils) and lymphocytes. Plasma cells were conspicuous in some animals. Many mesenchymal cells bore none of the characteristics of the above five cell types and we were unable to classify them. Eosinophilic and basophilic leukocytes, though seen fairly commonly in rabbits and in sinusoidal lumina of rats, were rarely observed in the periductular connective tissue of the latter species.

Lymphocytes and polymorphonuclear leukocytes tend to arrange themselves along the basement membrane of ductules (Fig. 11). They are usually separated from the latter structure by a few connective tissue fibrils. Only on one occasion did we observe a lymphocyte penetrating a ductular basement membrane though we failed to obtain satisfactory photographic evidence of this.

Both polymorphonuclear leukocytes and lymphocytes are found fairly frequently within the cellular

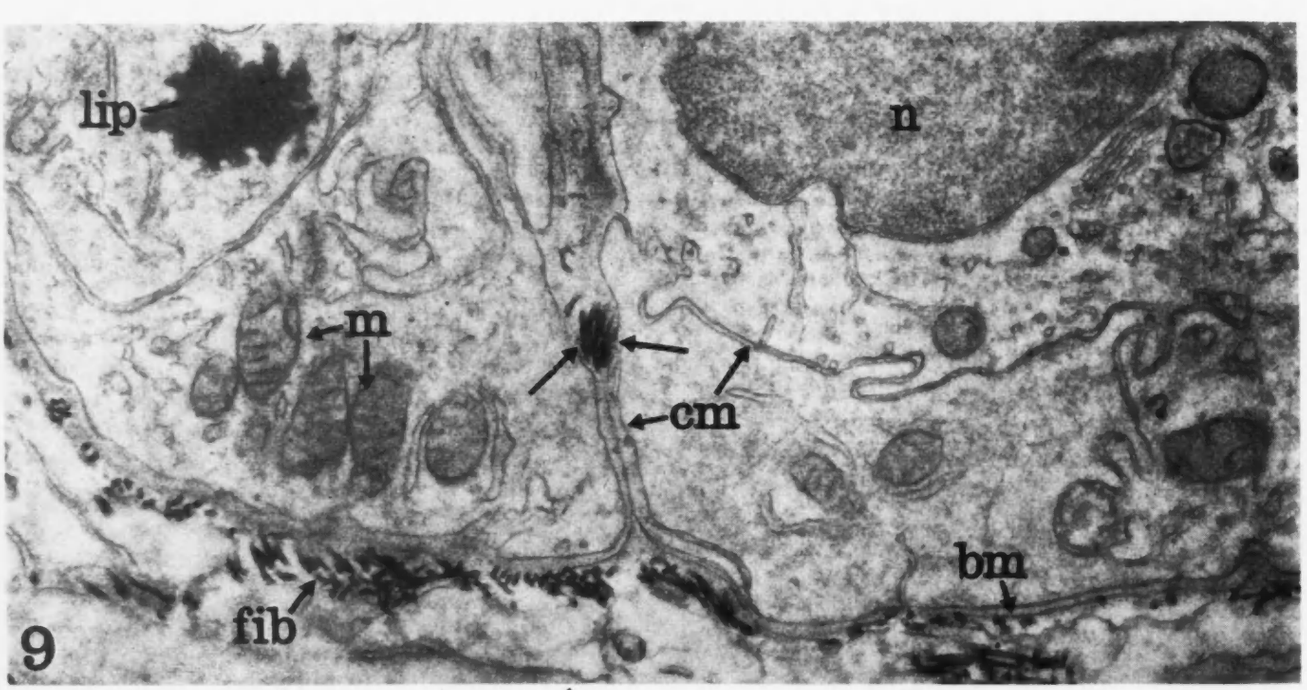

Fig. 9.—The anti-luminal margin of a bile ductule. The basement membrane and its accompanying connective tissue fibrils enter an indentation between adjacent biliary epithelial cells. Fibrils (unlabelled arrows) find themselves trapped in this pocket. Tangential sectioning makes recognition of the basement membrane difficult in some areas. Phosphotungstic acid, × 23,940.

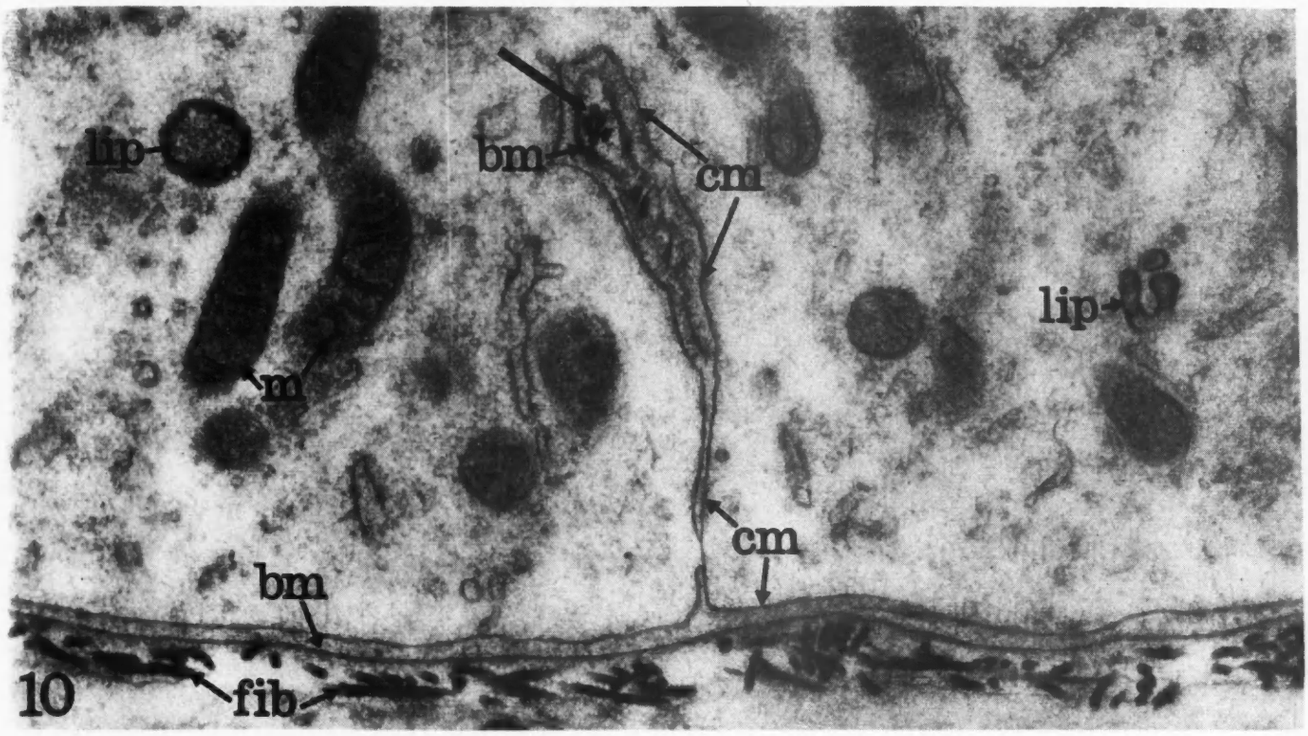

Fig. 10.—The appearance of trapped fibrils (unlabelled arrow) is similar to that seen in Fig. 9. The connection between the basement membrane of the anti-luminal border of the ductule and the fibrils in the pocket is not apparent in the picture. It is probably present in another plane of sectioning. This is an expression of the tortuosity of ductules. Phosphotungstic acid, × 29,200.

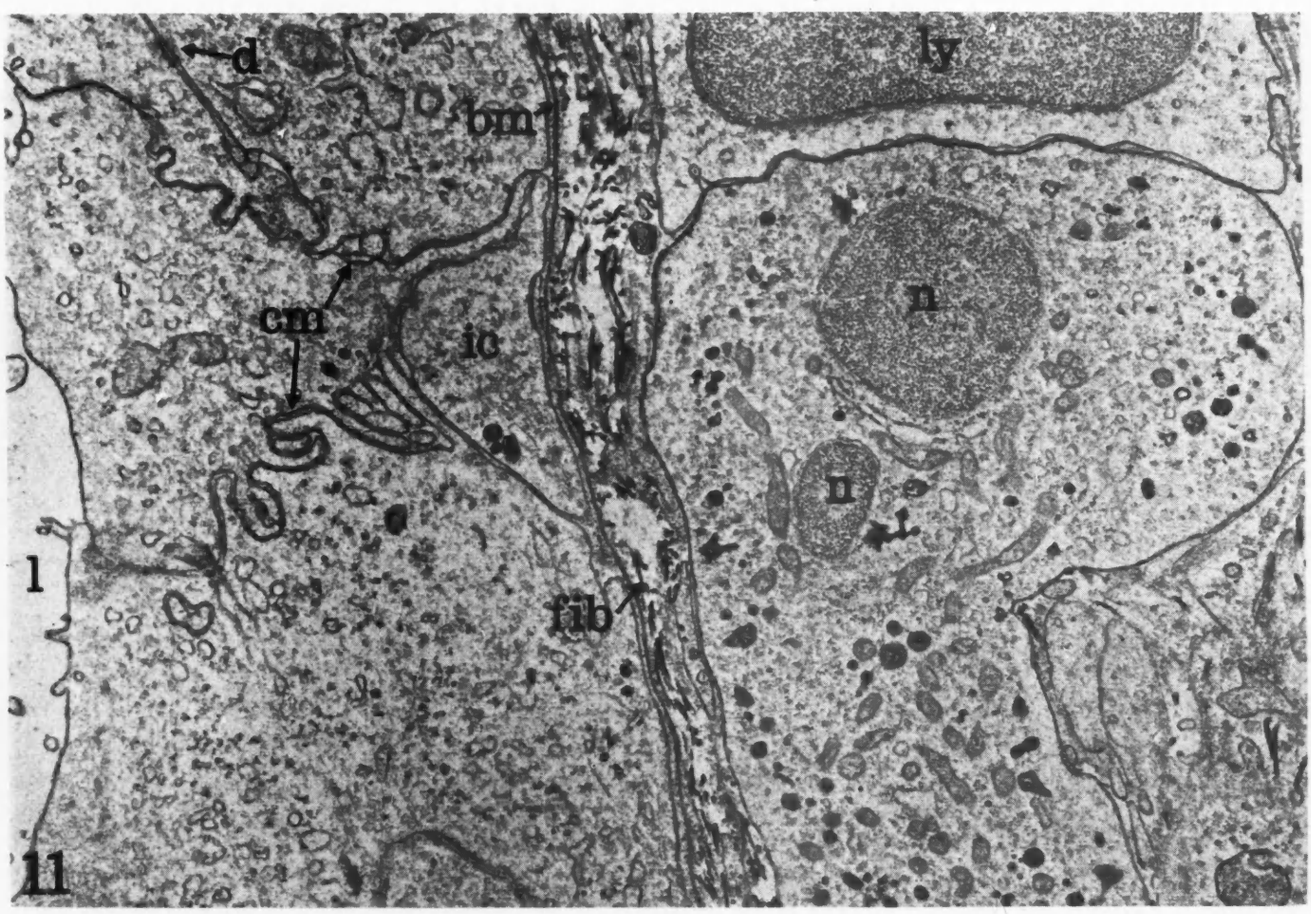

Fig. 11.—The lumen of a ductule is seen at the left margin of the micrograph. Its lining biliary epithelial cells are separated from the connective tissue envelope by a basement membrane. Beyond this a polymorphonuclear leukocyte and a portion of a lymphocyte can be seen. Compare this with Fig. 12. Phosphotungstic acid, × 16,800.

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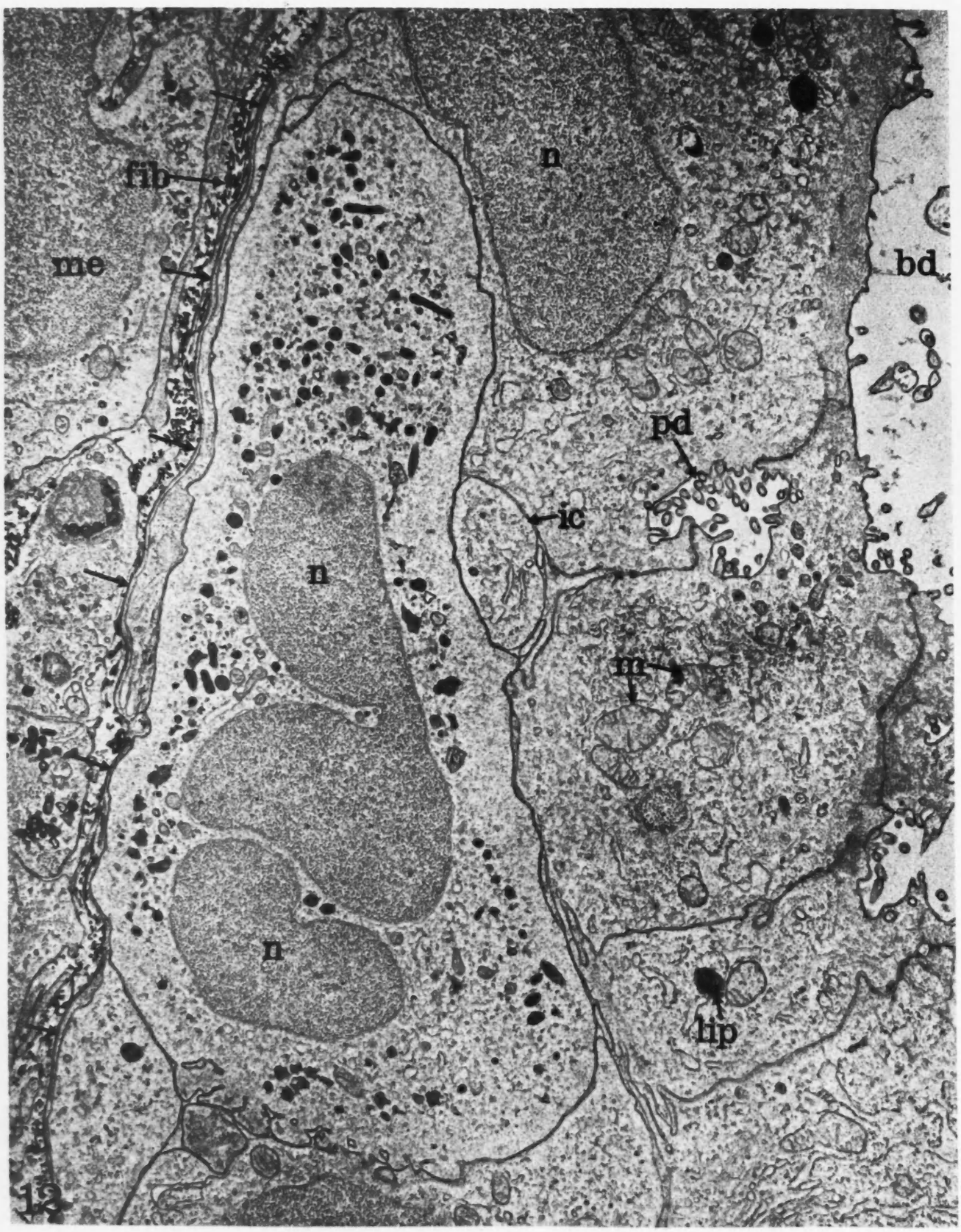

Fig. 12.—A ductular lumen is at the extreme right margin of the micrograph and its afferent preductule in the right centre. A polymorphonuclear neutrophilic leukocyte has penetrated through the basement membrane barrier (unlabelled arrows) and finds itself amongst the lining biliary epithelial cells. Phosphotungstic acid, × 15,900.

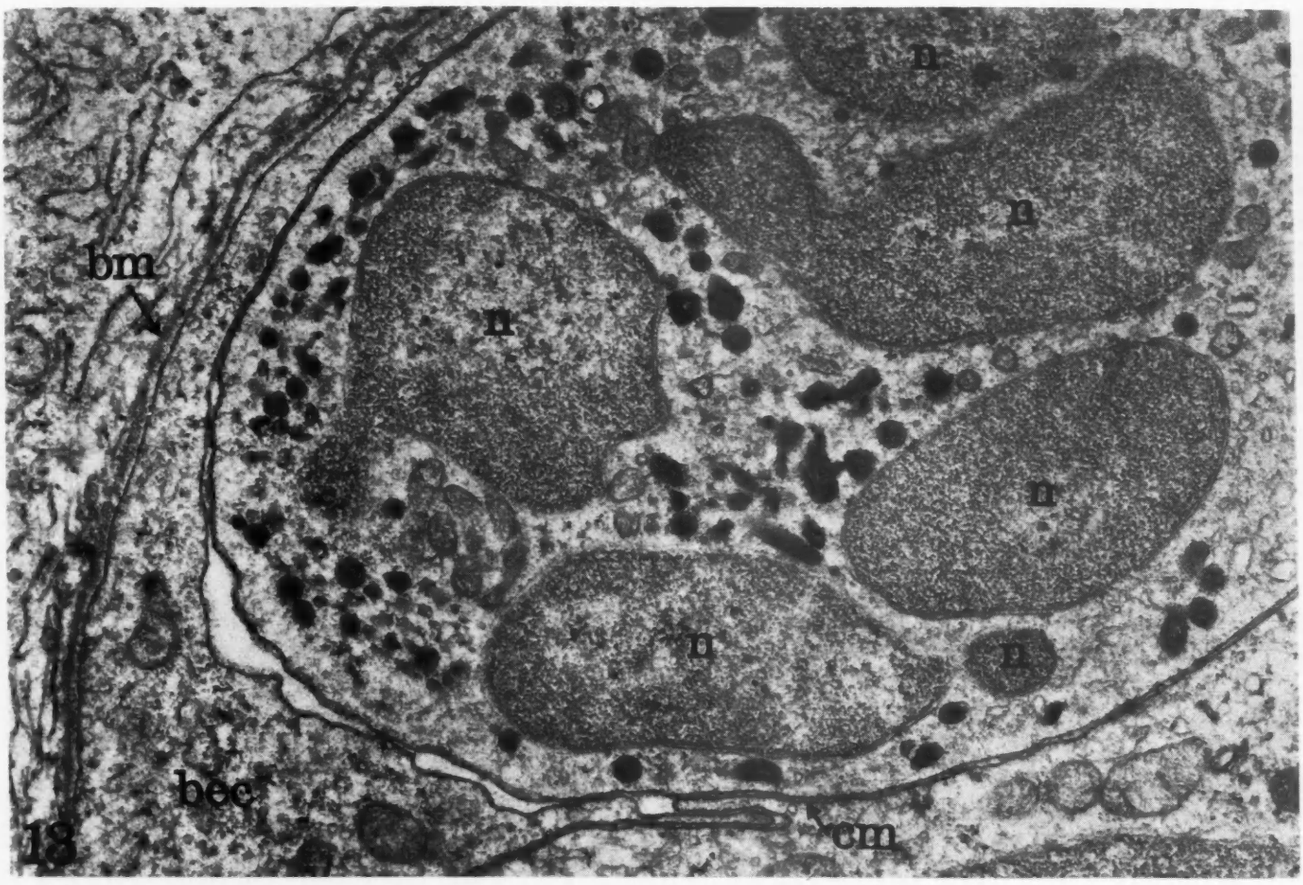

Fig. 13.—A polymorphonuclear leukocyte, with six distinct nuclear lobes, lies within the lining of a ductule. The basement membrane and the connective tissue envelope lie at the left margin of the micrograph. Processes of biliary epithelial cells hug closely the cell membrane of the neutrophil. Uranyl acetate, × 26,050.

wall of ductules (Fig. 12). When seen in a section which passed through the nuclei and the immediate perikaryonic cytoplasm, identification of such cells is relatively easy. When a section passes through the periphery of these cells, skirting their organelles and/or granules, differentiation between these and intercalated biliary epithelial cells may be difficult. Reliance must then be placed on the study of their limiting cell membranes which lack the interlocking projections of the latter. Even then differentiation cannot always be achieved.

Polymorphonuclear leukocytes occasionally reach the ductular lumen (Fig. 14). Some of these show evidence of injury, i.e. condensation of cytoplasmic matrix and reduction of granules. Bacteria were never identified in the lesions.

Discussion

Proliferation of bile ductules would seem to be a difficult point to prove at the magnifications employed in the electron microscope. We consider the most tangible evidence of this proliferative activity the marked increase of the observable points of contact between liver cells and biliary epithelial cells. This would indicate that many new connections between the lobular and extralobular pathways of bile conduction become established. We are not certain whether this interpretation is entirely correct, since we have observed points of contact between biliary epithelial cells and parenchymal liver cells where a biliary channel could not be seen in the plane of section.

We interpret the abnormal relationship between bile ductules and their connective tissue envelope, which we have observed, to be the result of an unusual tortuosity of these channels and their tributaries. The spurs and knuckles which project from ductules and which result from unusual transections of their profiles attest to this point. It is not surprising to find that connective tissue fibrils find themselves trapped in basement-membrane-enclosed pockets presumably at points where a portion of a ductular surface is indented as a result of kinking or branching of the main channel.

The cells which elaborate the basement membrane covering for the penultimate pathways of bile conduction are not known. It is, however, remarkable that not a single proliferated channel was seen devoid of this membrane. One cannot but suggest that the basement membrane is probably the product of biliary epithelial cells.

We consider it impossible to make a diagnosis of periductular fibrosis in the electron microscope. Connective tissue fibrils are normally present in this location. To assert that the number of these fibrils is increased seems to us impossible. We could not see bundles of a size larger than normal.

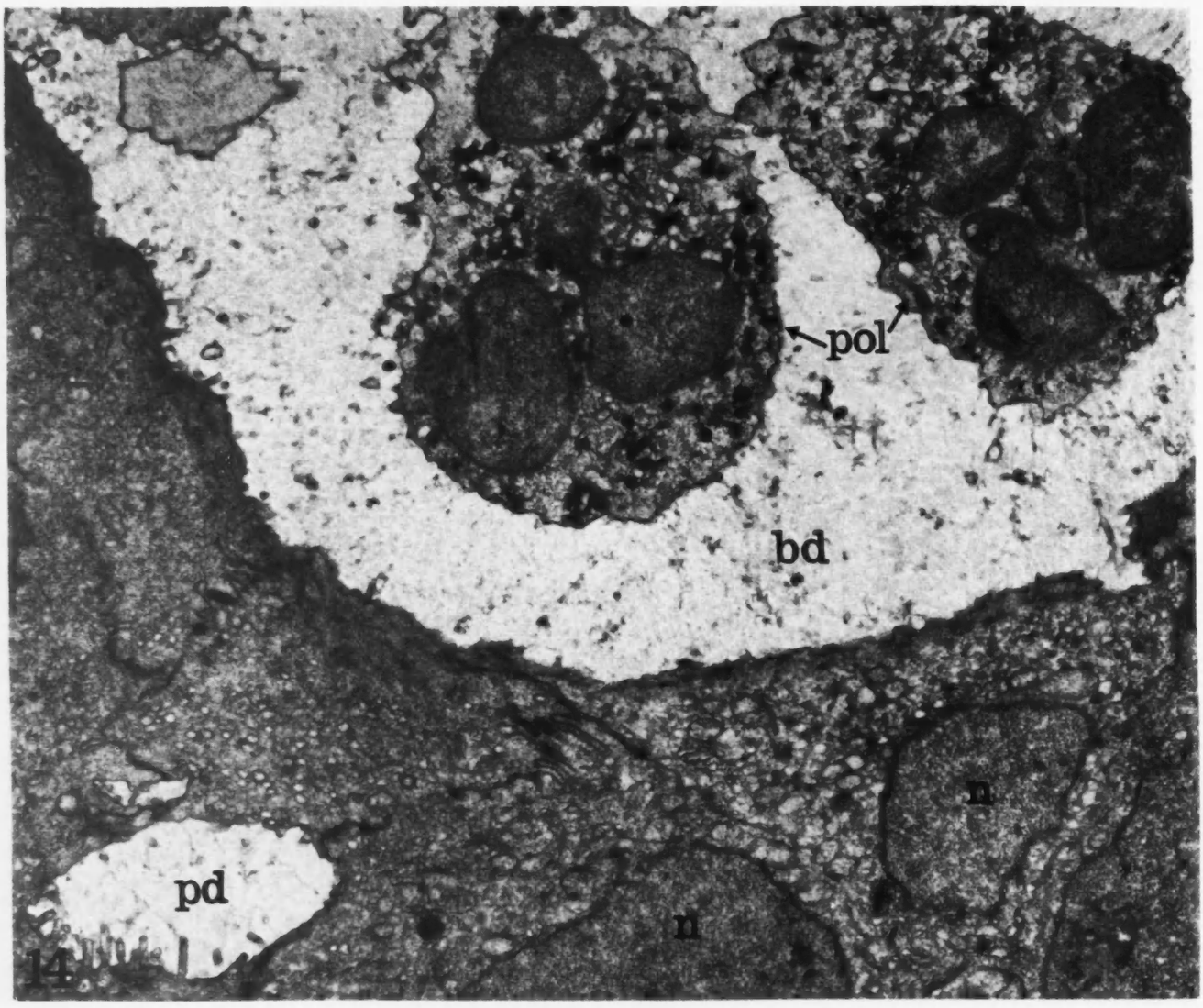

Fig. 14.—The lumen of a dilated ductule, almost devoid of microvilli, with its afferent dilated preductule. In the lumen of the former are two polymorphonuclear leukocytes which have penetrated the lining of biliary epithelial cells. Uranyl acetate, × 9600.

We therefore fail to aver the claims of others.[4] We are deliberately avoiding such terms as collagen, reticulin and elementary fibrils until the difficult problems of semantics pertaining to their designation have been resolved.

We have described evidence of a periductular and intraductular inflammatory reaction by virtue of the presence of polymorphonuclear leukocytes and lymphocytes outside the basement membrane, between biliary epithelial cells and within ductular lumina. Although we designate this as an inflammatory reaction, we have been unable to identify the presence of edema fluid in these areas. We have seen no evidence of vascular stasis and we know of no means of assessing vascular dilatation at an electron microscopic level of observation. We have been unable to identify any morphologic evidence of possible chemotactic processes or factors. Necrosis of biliary epithelial cells has not been seen in well-preserved tissue. The lumina of bile ductules are almost entirely empty and we must assume that they contain either no bile or bile in a form which is not electron-opaque. We have seen no evidence of extravasation of bile in the areas of inflammation. Bacteria could not be identified in our material. It is nevertheless possible that bacterial antigens may be present within ductular lumina and hence diffuse into the periductular tissues. The presence of large numbers of plasma cells in the periductular connective tissue of some animals would support this view. The possibility that amorphous components of bile stimulate the inflammatory reaction cannot be excluded.

SUMMARY

Proliferated bile ductules and preductules have been studied in rabbits and rats during the first 14 days after ligation of the common bile duct and in rats after prolonged administration of carbon tetrachloride. The presence of many more points of contact between biliary epithelial cells and parenchymal liver cells was

interpreted as evidence of proliferation of the penultimate pathways of bile conduction at an electron microscopic level of observation.

As a result of a marked tendency to branch and of excessive tortuosity of the penultimate channels of bile conduction, an abnormal relationship between biliary epithelial cells and their connective tissue envelope is frequently observed.

It was suggested that the presence of polymorphonuclear leukocytes and lymphocytes outside the wall, in the wall and within lumina of bile ductules represents an incomplete inflammatory reaction in response to unknown chemotactic influences.

The authors are indebted to Dean J. D. Hamilton for his helpfulness and encouragement and to Professor H. J. Barrie for his constructive criticism. Thanks are also due Misses B. Lambert and B. Main, as well as Messrs. G. Doornewaard and G. Thomas, for their untiring assistance and co-operation.

REFERENCES

1. CARRUTHERS, J. S. AND STEINER, J. W.: *Canad. M. A. J.*, **85**: 1223, 1961.
2. GRISHAM, J. W. AND HARTROFT, W. S.: *Lab. Invest.*, **10**: 317, 1961.
3. POPPER, H., KENT, G. AND STEIN, R.: *J. Mt. Sinai Hosp.*, **24**: 551, 1957.
4. POPPER, H. *et al.*: *Lab. Invest.*, **10**: 265. 1961.
5. SCHAFFNER, F. AND POPPER, H.: *Am. J. Path.*, **38**: 393, 1961.
6. STEINER, J. W. AND CARRUTHERS, J. S.: *Ibid.*, **38**: 639, 1961.

ACUTE BENIGN PERICARDITIS*

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DURING the period from July 1960 to February 1961, 10 cases have been seen at this centre consisting of a mild illness with variable symptomatology, but with sufficient clinical and electrocardiographic signs in each case to make the diagnosis of acute benign pericarditis. As there was epidemiological evidence suggesting that the disease was infectious, and as viral studies were undertaken in the majority of these cases, it is of interest to present the findings here.

CLINICAL FEATURES

The 10 patients ranged in age from 28 to 49 years. There were nine males and only one female, but this is probably no more than a reflection of the composition of this hospital's patient population.

All patients were admitted with the chief complaint of chest pain, in several cases of sufficient severity to warrant an admission diagnosis of myocardial infarction. This pain was described as lancinating, punctuated at intervals of hours to days by periods of dull, substernal aching. In the case of one of the authors (D.A.K.) there had been an episode of nocturnal pain with choking, sweating and angor animi on one occasion, ten days prior to diagnosis and admission to hospital. In the other physician, severe lancinating pains of momentary duration were noted in the left axilla before the onset of clinical pericarditis. In the intervals between the episodes of pain and for a period of months afterward, the patients experienced fatigue out of proportion to the activity undertaken.

The physical signs in all but two cases were limited to the presence of a pericardial friction rub. The duration of the friction rub varied from a few days in most patients to well over six months in one case. Tenderness of the chest wall or splinting of the chest with respiration was not observed, nor was a pleural friction rub detected in any of the cases, although pleuro-pericardial friction rubs were present in two cases. No evidence of cardiac enlargement, pulsus paradoxus, constriction of the pericardium, or decompensation were observed.

The electrocardiograms in all cases showed T-wave instability, and in a minority, only the transient R-T segment elevation in all leads except AVR, which has been accepted as the diagnostic early sign of pericarditis.

Treatment in each case consisted of bed rest, acetylsalicylic acid and penicillin; the last was administered until throat cultures in each patient were reported as showing no growth of hemolytic streptococci.

EPIDEMIOLOGY

A definite epidemiological connection could be traced between seven of the 10 patients involved. Cases 1, 2 and 3 were all soldiers serving in the same platoon, Cases 4 and 5 were physicians and Case 10 was a nurse from the ward where the three soldiers were treated. Case 6 was a clerk in the admitting department of the hospital. No connection could be found between Cases 7, 8 and 9 and the others in this series. A further interesting epidemiological point was that the brother-in-law of Case 10 developed an identical illness after Case 10 became ill. He was treated in another hospital and is not included in our series. There is thus fairly strong epidemiological evidence that these cases form a small outbreak of an infectious disease.

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LABORATORY FINDINGS

The results of general laboratory tests are shown in Table I. Throat swabs from all patients were examined bacteriologically except Cases 2, 3 and 7; in no case were hemolytic streptococci isolated. This, together with the fairly low antistreptolysin O (ASO) titres, which are shown in detail in Table I, suggested that the disease was not of rheumatic origin.

TABLE I.—LABORATORY DATA

Case number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Age	37	37	35	34	28	32	40	49	42	44
Leukocyte count	5000	10,500	7000	6000	10,000	8500	8500	10,500	19,000	7000
Sedimentation rate (mm./hr.)	24	34	15	15	7	10	27	30	21	7
Antistreptolysin "O" (Todd units)	50	12	..*	125	100	12	166	50	..	..

*Not done.

Virological investigation consisted of attempted virus isolation from specimens of throat washings and feces taken soon after admission, and the examination of sera, taken in the acute and convalescent phases of the disease, for antibodies to various enteroviruses.

Examination of the fecal specimens for the presence of Coxsackie viruses was done in this hospital by the inoculation of mice under 24 hours of age. The mice were observed for signs of paralysis and after three weeks were killed and examined histologically. These tests all proved negative.

Dr. N. A. Labzoffsky of the Virus Diagnostic Unit, Ontario Central Laboratory, carried out the other virological tests. The authors are most grateful for this most helpful co-operation. Stool specimens and throat washings were inoculated into tissue culture of monkey kidneys, human amnion and HeLa cells. Neutralization tests were carried out for serum antibodies to Coxsackie viruses A9, B1, B2, B3, B4 and B5 and to ECHO virus type 9.

The interpretation of the antibody titres of the sera presents difficulties. On the basis of the accepted standard, which requires a four-fold or greater rise from the acute to the convalescent stage as acceptable evidence of a concurrent infection, only the Coxsackie B4 antibodies in Case 2 and the ECHO 9 antibodies in Case 9 suggest infection by these viruses. The titrations of Coxsackie B4 antibodies in the sera of Case 5 were not taken to full titre, so that it is not known if a four-fold rise had occurred. However, the high levels in these sera do at least suggest a recent infection by this virus.

DISCUSSION

Although pericarditis has been recognized by pathologists for centuries, it was 1942 before the entity that is now known as acute benign pericarditis was separated from other types of pericarditis.[1] However, the association of pericarditis with an epidemic of Bornholm disease had been noted in 1933, when Bing[2] reported six cases. Not until 1958 were cases reported in which virus was recovered in the stool and a rise in serum antibody titre to the same virus demonstrated.[10]

The clinical picture in this disease is quite variable, although the majority of patients present with pain which is rarely severe enough to require morphine for relief. This pain is usually substernal or epigastric, but may localize to a small precordial area, well to the left of the midline. It is stated that deep breathing may aggravate the pain, but in one of the patients in the present series, maximal inspiration abolished the pain completely. The clinical differentiation of this symptom from the pain of an acute coronary occlusion may rest on relief of pain by such simple maneuvers. There may be short premonitory pains,[1] similar to a "stitch in

TABLE II.—VIRUS INVESTIGATIONS

Case number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Throat washings (tissue culture)	—	—	..	—	—	..	..	—	—	—
Feces (tissue culture)	ECHO 19	—	..	—	—	..	..	..	—	—
Feces (suckling mice)	..	..	..	..	—	—	—	—	—	—
Virus antibodies	—	B4	..	B2	B4	B3	B4	—	B4 32/32	A9
Acute/convalescent serum		0/16		32/64	>128/>256	16/32	64/128		E9 <16/32	32/32

.. = Not done.
— = Negative test.
B2, B3 etc. = Coxsackie viruses B2, B3 etc.
E9 = ECHO virus type 9.

The results of all these virological investigations are presented in detail in Table II. No isolations of Coxsackie viruses were made. The single isolation of ECHO virus type 19 most probably represents chance carriage of the virus at the time of the illness. Antibodies to this virus were not found in either acute or convalescent serum samples.

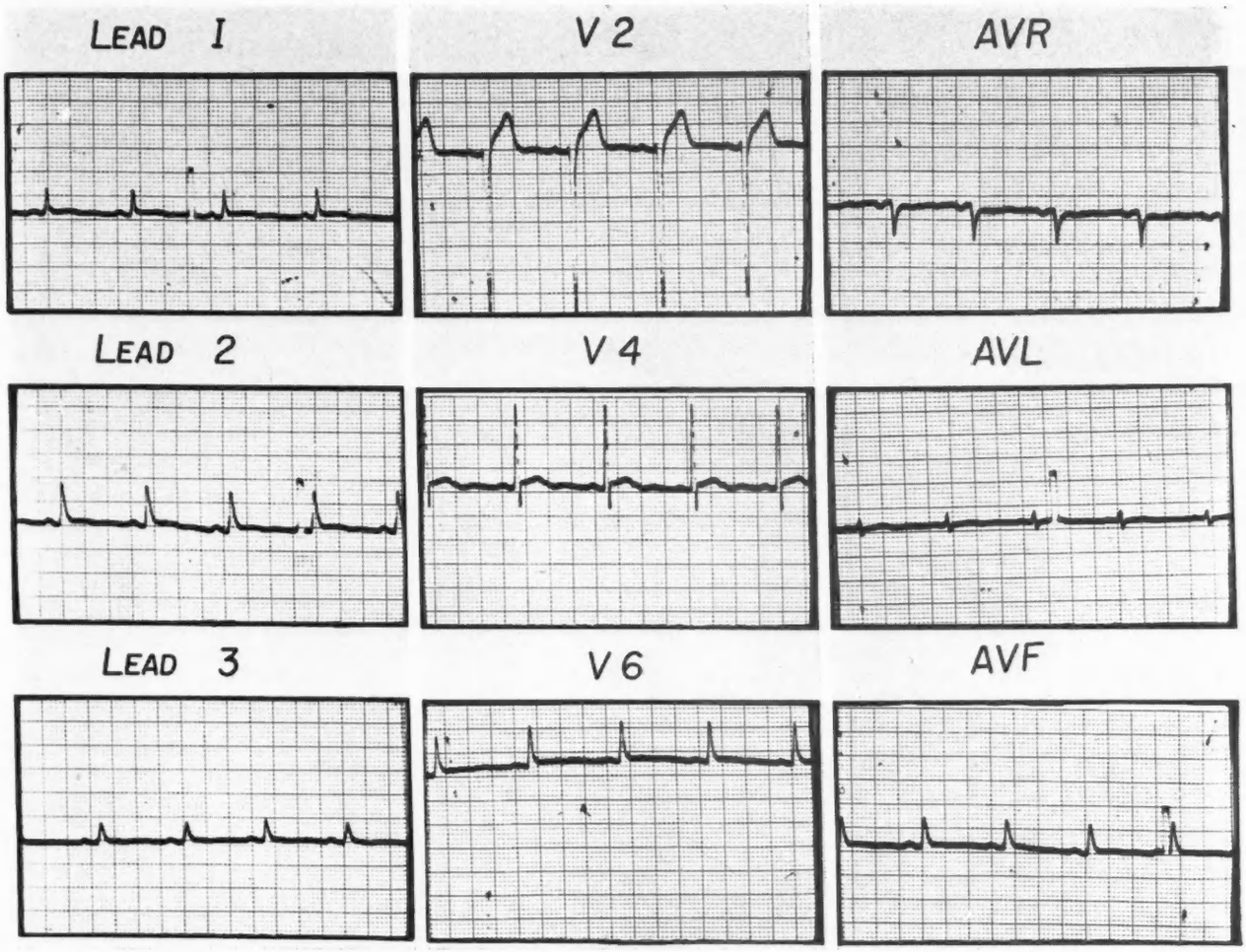

Fig. 1.—Electrocardiogram of Case 1 on admission, illustrating the classical electrocardiographic features of pericarditis. Note the depression of the ST segment in lead AVR, as emphasized by Singer.(12)

the side", that are differentiated from angina by their lack of relationship to effort. The association with an epidemic of pleurodynia[6, 11] may serve to focus diagnostic attention on acute benign pericarditis, if electrocardiographic changes are present.

A friction rub of varying duration may be heard in some, if not all, patients. In Case 10 of our series, the friction rub remained for longer than six months. It is only the short-lived pericardial friction rub which may cause confusion, as the friction rub associated with myocardial infarction is audible for only a few hours, rather than days. The temperature is usually over 99° F. and in our cases never exceeded 101° F., although temperatures up to 104.9° F. have been reported.[12] The leukocyte count may be normal or elevated;[12] in this series only 3 of 10 patients had a white cell count in excess of 10,000 per c.mm. The sedimentation rate is of little value and the antistreptolysin "O" titre rarely elevated. Although atrial fibrillation, paroxysmal atrial flutter and ventricular tachycardia have all been reported during the course of acute benign pericarditis,[12] the only arrhythmia which was observed in these few patients was a mild atrial tachycardia of up to 120 per minute.

Electrocardiographic changes may be delayed for several days, or may not occur at all.[8] However, nearly all cases of pericarditis are accompanied by some myocarditis of the subepicardial muscle layers,[7] producing the characteristic abnormality of ST segment elevation with the segment concave upwards or flat in all leads except AVR.[1] Singer[12] makes the point that depression of the ST segment of greater than 1 mm. in lead AVR early in the disease is diagnostic. The T-wave shortly becomes negative or flat and this is the stage at which our patients were usually seen (see Figs. 1 and 2). In the experience of the authors, the differentiation of pericarditis from recent myocardial infarction would have been difficult on electrocardiographic grounds alone. Electrocardiographic abnormalities may remain for long periods of time, and Godfrey[7] reported three cases with clinical and electrocardiographic evidence of myocardial injury seven months, one year and 2½ years after the acute episode. There is a variant of acute benign pericarditis which is sharply localized to one area. The electrocardiogram here may simulate that of acute myocardial infarction, even to the appearance of reciprocal ST segment depressions, but Q waves do not appear.[3]

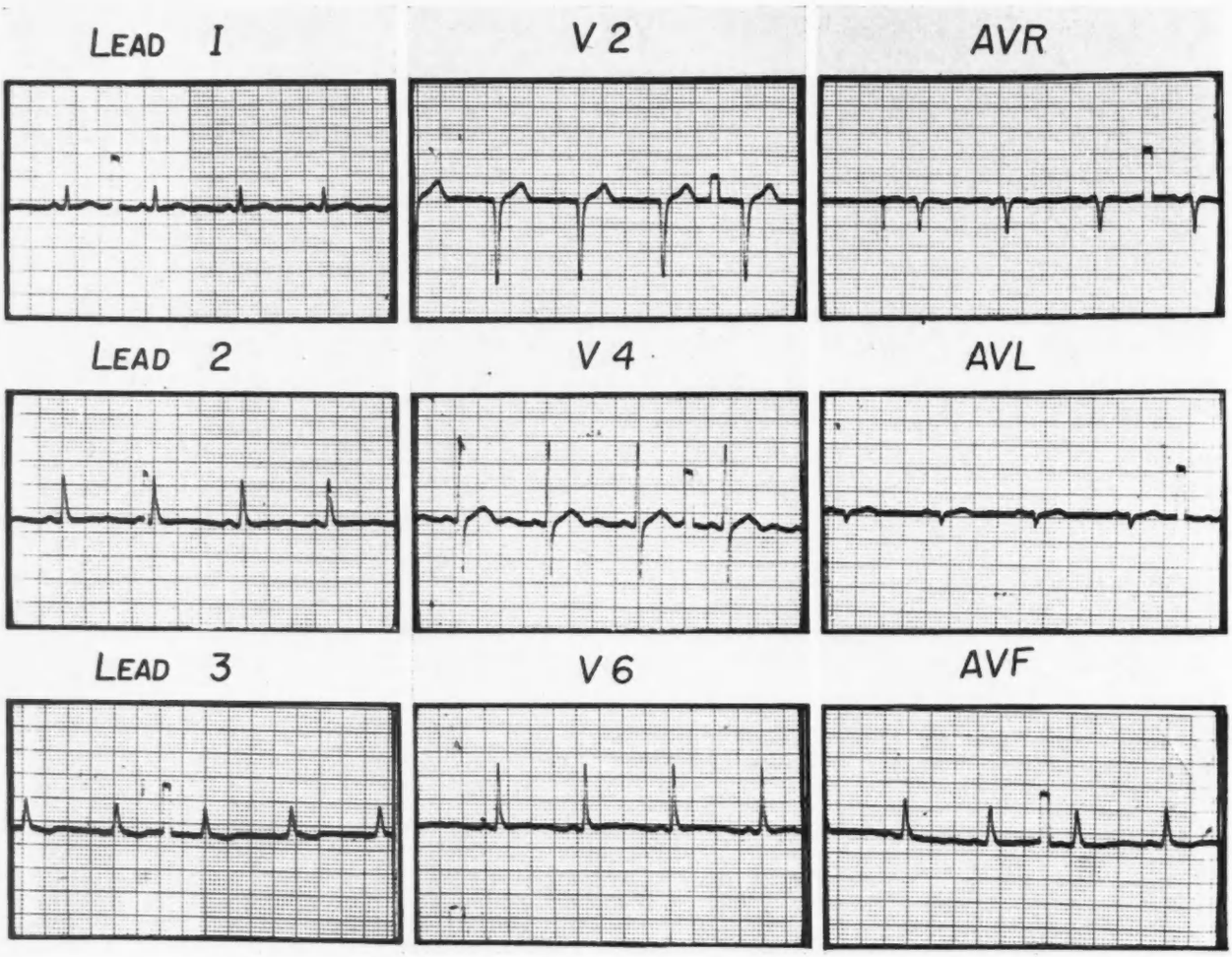

Fig. 2.—Electrocardiogram of Case 1, 48 hours after admission, illustrating the completely nonspecfic pattern which was more regularly observed in this series.

The most important aspect of treatment is strict bed rest. The patients with the longest history of symptoms before treatment required the longest period of convalescence in our series, as in those reported by Gillett.[6] Salicylates and penicillin were used empirically in all cases. Fremont and Volk[5] recommend the use of steroids in the treatment of patients with severe disease and for the treatment of recurrences, but these drugs were not administered in this series. Repeated mild chest pain is common but does not affect the prognosis,[1] which is uniformly good. However, a recurrence is common as late as eight to ten years after the first attack[12] and should be treated once again with bed rest and salicylates.

Because of the difficulty in defining the relationship of Coxsackie viruses to human disease, certain criteria were proposed by Kilbourne[9] in 1952. He considered that the diagnosis should rest on demonstration of an antibody response to a virus of the Coxsackie group and preferably the isolation of Coxsackie virus from the patient. These criteria were not fulfilled until 1958, when Movitt *et al.*[10] reported two cases in which the virus apparently responsible was Coxsackie B3 in one case and Coxsackie A1 in the other. In the period 1956-59 in Ontario there were only 27 virus isolations from cases of pericarditis;[4] all of these were Coxsackie B5. Woodward *et al.*[13] point out that it would be necessary to isolate the virus in high titre from the pericardium and to demonstrate a significant rise in serum titre of the appropriate antibody to provide convincing proof of the etiological relationship. So far these conditions have not been fulfilled.

Although, for epidemiological reasons, at least seven of our cases were probably caused by the same infecting agent, definite evidence that a single virus infected them all or even most of them was not found. If the seven cases, which were related epidemiologically, are considered alone, only two of them, Case 2 and Case 5, showed probable serological evidence of infection by Coxsackie B4; the other four whose sera were tested had no antibodies to this virus in their convalescent specimens. If the whole series of 10 is considered, two other patients had antibodies to Coxsackie B4 (this is indicative of some past infection with this virus) and another patient had no Coxsackie B4 antibodies in the convalescent serum. Thus the majority had no evidence of recent infection with this virus. The facts are insufficient to permit any definite conclusion about the etiology of this outbreak. If anything, it is more difficult to explain the total

lack of antibodies to the virus in the convalescent sera of so many of the patients if Coxsackie B4 is assumed to be the cause, than it is to postulate an undiscovered viral cause and to assume that the antibodies to Coxsackie B4 were due to the presence of Coxsackie virus, which was prevalent in the community at about the same time. Asymptomatic or trivial enteroviral infections can lead to great confusion when one is attempting to establish the etiology of unexplained diseases; because of the high prevalence of these viruses at certain seasons some people may have one of these viral infections and an unrelated serious illness coincidentally.

It is considered that these cases represent a definite clinical entity, quite distinct from Bornholm disease, and we do not feel convinced that the etiology of the disease is yet clearly proven. While other reports of individual cases strongly suggest that a Coxsackie virus was responsible, in the present small outbreak this may not be true and some other causative agent may exist.

SUMMARY

Ten cases of acute benign pericarditis seen within an eight-month period among members of the Armed Forces and in hospital personnel have been presented, along with a consideration of the clinical and electrocardiographic picture of the disease.

Acute benign pericarditis is a disease that may be confused with acute myocardial infarction, and the differential diagnosis on clinical and electrocardiographic grounds is stressed. The disease appears to be infectious because four of the ten cases occurred in hospital personnel in contact with the remaining cases. No clear-cut evidence was obtained that the cases were all caused by Coxsackie viruses, and the connection of these viruses with the disease is discussed.

ADDENDUM

Since this paper was submitted for publication, seven additional cases have been seen; five of these were among Armed Forces personnel. Coxsackie B5 was isolated on tissue culture from feces from three of these, but complete studies are not yet available.

The authors wish to thank Dr. N. A. Labzoffsky, Ontario Central Laboratory, for the performance of tissue cultures and neutralization tests and Dr. E. A. Fergusson, Hospital Superintendent, for his co-operation in the preparation of this paper.

REFERENCES

1. BARNES, A. R. AND BURCHELL, H. B.: *Am. Heart J.*, **23**: 247, 1942.
2. BING, H. I.: *Acta med. scandinav.*, **80**: 29, 1933.
3. BULLINGTON, R. H. AND BULLINGTON, J. D.: *J. A. M. A.*, **171**: 2205, 1959.
4. COOPER, M. R. *et al.*: *Canad. M. A. J.*, **84**: 200, 1961.
5. FREMONT, R. E. AND VOLK, B. W.: *Dis. Chest*, **36**: 319, 1959.
6. GILLETT, R. L.: *New England J. Med.*, **261**: 838, 1959.
7. GODFREY, J.: *Ann. Int. Med.*, **35**: 1336, 1959.
8. JAMES, T. N.: *South. M. J.*, **52**: 1391, 1959.
9. KILBOURNE, E. D.: *Am. J. M. Sc.*, **224**: 93, 1952.
10. MOVITT, E. R. *et al.*: *New England J. Med.*, **258**: 1082, 1958.
11. NULL, F. C., JR. AND CASTLE, C. H.: *Ibid.*, **261**: 937, 1959.
12. SINGER, M. M.: *Am. Heart J.*, **58**: 568, 1959.
13. WOODWARD, T. E. *et al.*: *Ann. Int. Med.*, **53**: 1130, 1960.

CHRONIC PARONYCHIA: REVIEW OF SEVENTY CASES

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PARONYCHIA is an inflammatory disease of the tissues surrounding the nail plate. The term perionychia was preferred by Hellier,[1] but paronychia appears to have received general acceptance.

There has been considerable disagreement about the etiology of chronic paronychia and particularly about the role of monilial and bacterial organisms in the pathogenesis of this condition.

Whittle and his colleagues[2] considered the etiological aspects in 104 cases; 96 were women, 50% of whom were between 40 and 60 years old. The right middle finger was most frequently the first digit to be affected. This review appears to show, and our observations appear to support, the following as a reasonable explanation of the pathogenesis of chronic paronychia.

Some form of chemical or physical injury to the cuticle leads to subcuticular infection and to the formation of a subcuticular abscess. If the infecting organism is *Staphylococcus aureus*, the disease is likely to be more acute and painful; if it is *Candida albicans*, the disease is likely to be more indolent; a distinction, however, cannot be made on clinical grounds.

The subcuticular infection leads to destruction of the eponychium and to inflammatory edema of the nail fold. This edema causes a pillow-like swelling of the nail fold and separation of the nail fold from the nail plate. The blind pocket between the nail fold and the nail plate is then subject to further infection. Rough and wet work is an important factor in the etiology, both by causing the original cuticular injury and by promoting maceration and infection of the pocket.

A mycological and bacteriological review by Marten[3] appears to show clearly the nature of the infection of the pocket. He cultured *Candida albicans* from the nail folds of 33 of 34 patients with chronic paronychia, a much higher incidence than in other reported series. In 29 patients, *Escherichia coli*, and in 20 patients, *Proteus vulgaris*, were also isolated. Evidence that these organisms originated

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from the gut was produced by recovering identical strains of Proteus from the nail fold and from the feces. From these and associated findings he provided convincing evidence that the feces and mouth provide a reservoir from which the nail fold is infected in chronic paronychia.

Review of our series of patients with chronic paronychia was undertaken to establish the age, sex and occupation of those affected, to assess the various etiological factors, and to suggest a therapeutic approach because successful management is often difficult.

CLINICAL MATERIAL

The records of 70 patients seen in the private practice of one of us (J.C.M.) were reviewed. Chronic paronychia may be secondary to a systemic condition such as Raynaud's disease, or a complication of pompholyx or dermatitis venenata of the fingers; since the management is that of the primary condition, patients with secondary paronychia were excluded from the study. Sixty-six of the 70 patients

TABLE I.—INCIDENCE OF CHRONIC PARONYCHIA BY AGE

Age in years								
0-9	*10-19*	*20-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70-79*	*80-89*
5	4	6	22	16	7	7	2	1

with primary chronic paronychia were seen on referral for dermatological management after a period of treatment by their physicians. Therefore, the group was possibly unrepresentative; these patients had been selected because of chronicity and refractoriness to treatment. In 67 cases paronychia was the problem which caused the patient to seek advice and in three cases paronychia was noted during general examination of the skin. The fingers were affected in 69 cases and a toe in one case (a female child).

TABLE II.—INCIDENCE BY OCCUPATION

Housewife	43
Student (3 males, 6 females)	9
Nurse	7
Teacher	2
Stenographer	2
Dental assistant, fish canner, laboratory technician, waitress, cheese wrapper, dietitian, lumberworker (male) ..... each	1
Total	70

Table I shows that the condition was most common in young adults and in the middle-aged.

TABLE III.—SIDE AND DIGITS AFFECTED

Right	27 (fingers 26, toe 1)
Left	15
Both	23 (all fingers affected in 6)
Not recorded	5
Total	70

There was a striking difference in incidence according to sex; four males (three children and one adult) and 66 females (six children and 60 adults) were affected. The occupation of the 70 patients was important and is shown in Table II.

TABLE IV.—DIGITS AFFECTED

R1	R2	R3	R4	R5
20	17	23	24	12
L1	L2	L3	L4	L5
16	16	18	20	13

Not recorded 5 patients.
R1 toe—female child.

The side and digits affected are listed in Tables III and IV. The digits listed are those which were involved at the time of examination and not necessarily those which were involved first in the course of the illness. There was often a history of involvement of other fingers in the past. The duration of the disease is summarized in Table V.

TABLE V.—DURATION

Less than 1 month	*1 - 3 months*	*3 - 6 months*	*Over 6 months*	*Not recorded*
3	14	17	33	3

CLINICAL FINDINGS

An affected finger showed a moderately tender, edematous, dull erythematous swelling of the nail fold with the formation of a pocket between nail fold and nail plate. A probe could be inserted into the pocket for up to 4 mm. In some cases seropurulent discharge could be expressed or milked from beneath the posterior or lateral nail fold. More often, however, although there was a history of recurrent slight discharge, no moisture could be expressed at the time of the examination. The nail usually showed transverse ridging either of the whole or of a proximal portion of the nail plate corresponding to the length of the history. In this case, the distal portion of the nail was healthy and no subungual debris was seen. If only a portion of the nailfold was involved, only an equivalent portion of the nail plate showed changes. The ridged nail often showed some discoloration, light or dark brown or rarely green, but was of good lustre, firm and not friable, in contrast to the crumbling and disorganization of the nail plate in onychomycosis (tinea unguium). Two patients showed erosio interdigitale blastomycetica, a monilial infection of the third and fourth finger web. The nail fold was more or less inflamed and edematous at the time of examination, and the nail plate was more or less ridged and variably discoloured, but the pathognomonic finding was the presence of a pocket between nail fold and nail plate (Fig. 1). The eponychium was absent and the cuticle had separated from the nail plate (Fig. 2).

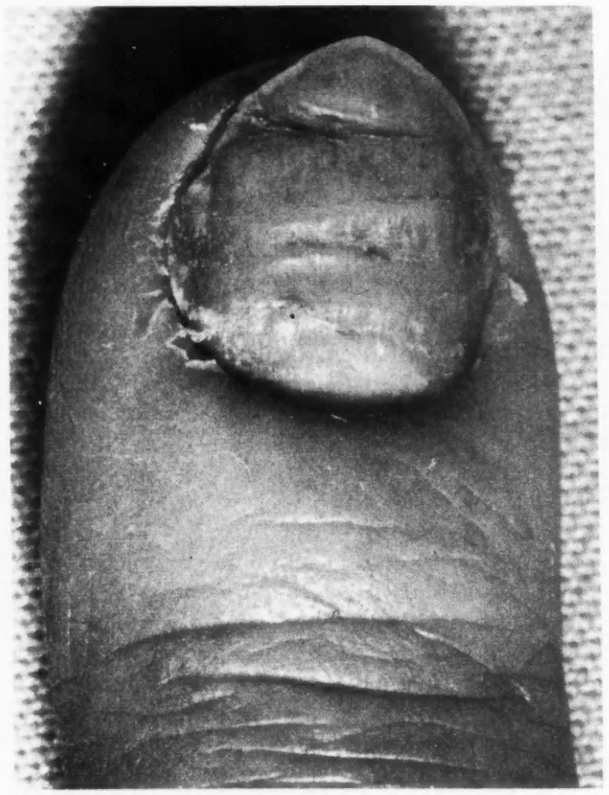

Fig. 1.—The nail in chronic paronychia. Note the pocket between the nail fold and nail plate.

These changes are quite distinct from those of onychomycosis. In this fungus disease of the nail there is primarily disintegration of the nail plate which starts at the distal end and spreads proximally; paronychia is not seen except in rare and severe cases of tinea in which the nail matrix is invaded.

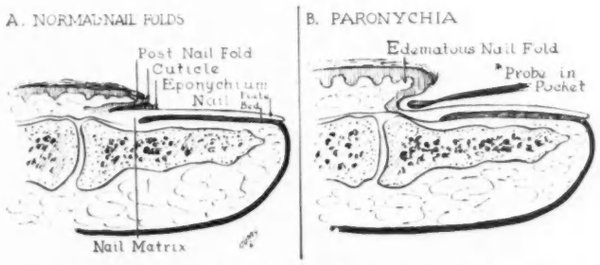

Fig. 2.—A diagram of the normal nail and the nail in chronic paronychia showing the pocket between the nail fold and nail plate.

ETIOLOGICAL FACTORS

With the exception of eight of nine patients in the 0-19 age group, all the patients in this series gave a history of frequent exposure to wet work. The adult male patient in the series was a lumber worker (log faller) whose attack began during prolonged wetting of his hands during work in the bush. The following aspects of the history were especially studied as relevant to the etiology.

Several patients noted the onset after bottling fruit and canning in the summer, after making dough for bread, and after minor gardening injuries followed by scrubbing soil from the nails.

Many patients gave a history of vigorous manicuring and of subjecting the cuticle and eponychium to picking, biting, or cutting with a razor blade. Pushing the cuticle back after washing the hands was a common point in the history. Some patients used liquid "cuticle remover". One patient, in whom the disease was of 10 years' duration, manicured twice weekly and had a compulsive habit of picking and biting at the frayed eponychium. In some patients the onset appeared to follow use of strong detergent solutions or cleansing chemicals which made the nailfolds sore. Physical trauma to the fingers precipitated the onset in six patients. The involvement of the great toe in a child followed trauma.

In view of the possibility of contamination from monilial vaginitis, inquiries were made about vaginal discharge and irritation. However, vaginal examination was carried out only if the history provided a lead to this investigation. It was not considered certain in any of these cases that infection from the vaginal tract was a factor in the onset of the paronychia, but an association was suspected in three adults. In the case of a 3-week-old female child paronychia of the left third and fourth fingers accompanied dermatitis venenata and probable moniliasis of the diaper region.

The effect of nail polish was difficult to assess, but an impression was gained that frequent use of nail polish remover was a relevant factor. Application of nail polish that was then left on and painted over rather than removed frequently did not appear to be significant.

Thirteen patients complained of undue numbness, blanching and coldness of their hands in the winter and from exposure to cold. Chilblains are a distinct rarity in Canada, in contrast to their commonness in English dermatological practice; two patients gave a history of chilblains in England.

DISCUSSION

The striking age, sex and occupational incidence in this series supports the view that chronic paronychia is a disease of those involved in wet work. The age group most affected was a decade younger than in Whittle's series. Whittle raised the question whether the overwhelming preponderance of women in his series was also noted in North America, where much of the washing of dishes and clothes is done by machinery. Our series shows the same female preponderance. North American males are more exposed to dishwashing than English males, and in British Columbia there are two male occupations in which prolonged wetting of the hands is common, namely, fishing and logging. It is difficult to believe that wet work alone explains the female preponderance, and since a fecal rather than vaginal source of Candida is suspected, the remaining sexual difference lies in the frequency of manicuring and in the

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use of nailpolish. It is our belief that damage to the eponychium and cuticle by manicuring is an important factor in the pathogenesis.

The condition rarely affects the toes. The right hand was more often affected than the left, and the right ring and middle fingers were most frequently involved. The right hand is more subject to inexpert manicuring and to fecal contamination in right-handed persons. It is difficult to assess the relative importance of the other factors noted, but it is likely that chemical injury from occupational irritants and physical injury from manicuring damage the cuticle, and inflammatory edema of the nail fold results in swelling and the formation of a pocket. This pocket is then subject to further infection and to the same hazards (including moniliasis) as a moist skin fold elsewhere. The information in this series is deficient in that bacteriological studies were not made regularly. The absence of this evidence is due to our belief that, from the practical therapeutic point of view, treatment should keep the diseased area, with its subcuticular pocket, dry and sterile whatever organisms are present. Pus which exudes from under the nail fold may be easily obtained for culture, but it is difficult to know what specimen to take in office practice in the case of a dry paronychia. Marten[3] obtained debris with a moist swab inserted deeply into the pocket and immediately plated out on Sabouraud's dextrose agar. Scrapings of the nail are not a reliable source of information.[2] The disease is primarily an inflammation of the perionychial tissues, and ridging of the nail is a secondary change due to inflammatory disturbance of growth of the matrix. In some of our cases bacteria were cultured; in other cases Candida was cultured early in the illness, and subsequently Candida or a varied bacterial flora or no growth was reported from a dry swab.

Therapy

All patients were using some form of treatment at the time of examination, the great majority under medical advice. Eight patients had had one or more nails removed surgically, and paronychia had persisted during and following regrowth of a new nail. Some patients had received griseofulvin therapy without benefit. Many patients were using hot water soaks; this form of treatment might have relieved pain during the development of acute paronychia, but in chronic paronychia it had not seemed to be helpful.

The chemically simple and economical management which is outlined below was found to be most likely to be effective. It is designed to maintain dryness and sterility and to promote closure of the subcuticular pocket. It is not always well accepted at first, because it contains more negative than positive advice.

In the presence of much pain and discharge, rest with elevation of the hand in a sling is necessary. When the patient's occupation outside the home appears responsible, a period away from work is usually required. Strict avoidance of immersion of the affected finger in water for two weeks and minimal exposure thereafter is advised. This may be achieved by wearing cotton under rubber gloves and by following the advice given to patients with dermatitis venenata caused by multiple household irritants.

Where one or a few fingers are affected, rubber finger cots slipped on before wet work may be tolerated better than gloves. If a patient complains that the wearing of gloves involves the hazard of dropping a slippery baby, she may wear a cotton glove over a rubber glove. A mop is useful for the dishes. Strict avoidance is advised, until cure is achieved, of exposure to bleach, strong detergent solutions and harsh cleansers. The patient may avoid meat, fruit and vegetable juice by such tricks as holding a tomato with a fork rather than with a hand when cutting, and using a piece of cloth around the hand for squeezing oranges, and handling meat, etc. The patient should avoid manicuring and pushing back, biting, cutting or picking at the cuticle and eponychium, and she should not use liquid "cuticle remover". She should not clean out the pocket between nail fold and nail plate, and should cease pushing cotton wool and therapeutic agents into the pocket if this has been previously advised.

If local heat relieves tenderness, that from a hot water bottle or heat lamp is definitely preferable to hot water soaks. If nail polish is to be used, it should be painted over repeatedly rather than removed. She should visit the beauty parlour or obtain help for shampoos.

Topical Therapy

A solution of 5 parts of resorcinol made up to 100 parts in isopropanol is used. It is painted on the nail folds three times daily. It is not necessary to push this liquid under the nail fold, since it runs under readily.

Two weeks of treatment usually results in early resolution as shown by a marked lessening of tenderness, redness and puffiness of the nail fold. At this point an agent which is both antibacterial and antimonilial contained in a water-immiscible grease is used, and restrictions on wet work are relaxed. The agent iodochorhydroquinoline (Vioform), 3 parts made up to 100 parts in white petroleum jelly, is massaged into the nail fold and nail three times daily and applied to the nail fold before wet work.

Surgical Measures

These are rarely required but are necessary in two situations:

1. Cure is achieved when the cuticle readheres to the nail plate and the pocket is obliterated. All

measures should be designed to achieve this result and surgical interference may delay this readherence. In occasional cases, the cuticle readheres to the nail plate but a blind pocket remains under the posterior nail fold and it is necessary to free up the cuticle to establish drainage. The usual measures are then used again to sterilize and to dry the pocket until it closes.

2. Occasionally pus tracks under the nail plate into the nail matrix, leading to a subungual abscess. Removal of a portion of the nail plate is then necessary to allow drainage of loculated pus.

SUMMARY

A series of 70 patients with chronic paronychia is reviewed. Four males and 66 females were affected. Forty-three of the 61 adults in the series were housewives. The roles of chemical and physical trauma to the nail folds and of wet work were studied. It was concluded that damage to the eponychium and cuticle by manicuring was a prominent factor in the pathogenesis. The basic disorder was considered to be infection following physical or chemical trauma. Inflammatory edema caused the formation of a pocket between nail fold and nail plate, and whether this pocket was infected by monilial or bacterial organisms did not affect the basic treatment which was to keep the pocket dry and sterile. An outline is given of management designed to achieve this result.

The author wishes to thank Mr. V. E. Doray, Director of the Department of Medical Illustration, University of British Columbia, for his assistance with illustrations.

REFERENCES

1. HELLIER, F. F.: *Brit. M. J.*, **2**: 1358, 1955.
2. WHITTLE, C. H., MOFFATT, J. L. AND DAVIS, R. A.: *Brit. J. Dermat.*, **71**: 1, 1959.
3. MARTEN, R. H.: *Ibid.*, **71**: 422, 1959.
4. PILLSBURY, D. M., SHELLEY, W. B. AND KLIGMAN, A. M.: Dermatology, W. B. Saunders Company, Philadelphia, 1956, p. 641.

REVIEW ARTICLE

VIRUS INFECTIONS OF THE RESPIRATORY TRACT*

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INTRODUCTION

VIRUS infections of the respiratory tract are at present a bit of a muddle to the clinician. This confusion exists despite the valuable work which is done by virologists and epidemiologists in describing the occurrence in the community of an increasing number of virus infections. It would indeed be the simplest way to begin by showing the considerable list of viruses which are now known or suspected to cause respiratory disease, and, of course, the completion of such a list is obviously a fundamental need. Nevertheless, to the clinician, there is a sense in which the ever-enlarging list of causes may be likened to the way in which an expert can fill in a jig-saw puzzle with the picture face down upon the table. The completion of the jig-saw in this way represents a masterly piece of expertise but may give little satisfaction to the onlooker who likes to see the emerging picture.

At least part of the clinician's confusion is due to two main difficulties:

(a) Firstly, when a particular virus is originally isolated and studied, it is often associated with an outbreak of infection which bears a particular pattern. But, within a short time, it more often than not emerges either that the pattern becomes less clearly defined or that other viruses are discovered which produce a similar picture. With some notable exceptions indeed many agents produce symptoms and signs which make accurate differentiation between them on clinical grounds difficult if not impossible.

(b) A second difficulty is that identification of a virus as the cause of a particular infection takes time—in fact it is often a difficult virological exercise. A precise etiological diagnosis, therefore, must usually be retrospective: the cause is discovered after the patient has recovered. From this point of view the clinician usually works in the dark, for the virologist may give him little assistance in the diagnosis of the individual case.

There may, therefore, be some excuse if the clinician sometimes feels that, as more virus causes are discovered, he extends his knowledge without improving his understanding. The multiplicity of causes has been clearly demonstrated; the way in which these operate in man is less frequently emphasized. It has, therefore, seemed that it may be advantageous to approach the subject purely as a clinician groping for a clearer understanding. This may best be done first by discussing certain aspects of the host-parasite relationship in respiratory virus infections, and second by drawing attention to some of the remaining problems.

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I. THE HOST-PARASITE RELATIONSHIP

In virus infection, of course, the host is the cell. But the derangement of cell metabolism which results from the acceptance of the virus is so often followed by the disruption of the cell that we may easily overlook the fact that all viruses do not reach the cells of the respiratory tract in the same way. There are at least two main pathways. Although this will seem to the scientist an over-simplification it may form, for the clinician, a useful starting point from which some general conclusions may be drawn.

(a) *"Local" Virus Infection*

The commonest route of infection is for virus to enter in the respired air (Fig. 1). Direct exposure of mucosal cell to virus by droplet infection would seem to be the pattern accepted, for example, in influenza. For such infection to be successful two things are essential—the dose of virus must be adequate and the cell must be prepared to accept it. So far as dosage is concerned there are no guides to the necessary amount; but the kinds of symptoms and signs produced in the infected patient—the sneezing and coughing—probably ensure that under ordinary circumstances close contact presents an adequate dose to the unfortunate susceptible. Nevertheless clinical experience suggests that there must be wide variation in the required dose for different individuals. In some cases contact is short and slight and might suggest that small doses can be successful in infecting highly susceptible cells. But in others—e.g. among doctors—one finds many instances where frequent exposure under the ordinary conditions of practice fails and infection is only successful when very close contact with infection—perhaps the wife of the doctor or several members of his family—produces circumstances that overwhelm the resistance.

On the other hand, it seems likely that cells must be "prepared" for virus acceptance. This brings into prominence the resistance of the cell to infection and one or two aspects may be considered. Changes in the character of the mucus must be relevant in facilitating the attachment of virus to the cell. Is it in this respect that climatic change plays such an important part in the occurrence of infection? The demands which must be made upon the upper respiratory passages in warming and moistening the inspired air to the correct temperature and humidity for gaseous exchange in the lungs must be considerable having regard to the sudden variations which are constantly occurring in the ambient air. Such changes must surely affect the microchemistry of the respiratory secretions and might produce conditions (e.g. even such as change of pH) which facilitate virus attachment. Indeed the whole question of climatic change and virus implantation requires re-examination in view of the fact that certain of the "new" respiratory viruses seem to grow best at low temperatures.

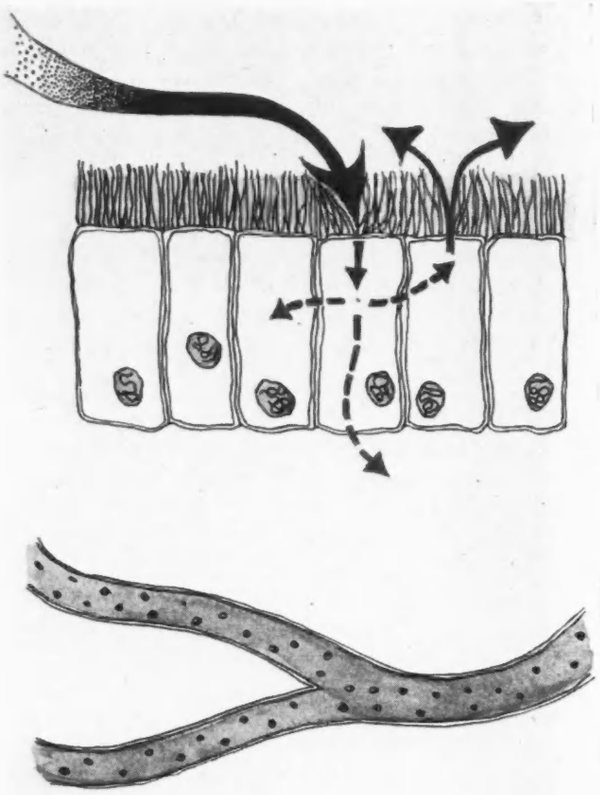

Fig. 1.—Local infection.

The nutrition of the host and his cells would also seem important. Certainly in the artificial conditions of *in vitro* experiments slight changes in the nutrition of the cell can greatly modify the effect of inoculated virus. Minimal alterations may result not only in failure of the virus to infect but in inability to demonstrate cytopathic effect. It seems at least possible that as the level of human nutrition improves—a condition which might be expected to enhance resistance to bacterial infection—the cell becomes a better supporter of the needs of virus metabolism so that its susceptibility to virus infection is enhanced.

If viruses can produce a variety of respiratory infections by local implantation, certain broad deductions may be drawn. A feature of infections of this type should be that direct action would rapidly produce damage, and, therefore, symptoms and signs. The incubation would thus be short. But, if virus makes a direct approach to superficial respiratory cells, serological immunity may be relatively unimportant. Indeed it is not too paradoxical to imagine that a host who could be regarded as resistant in the immunological sense might have susceptible cells. Further, if infection is direct, one should not expect too much from forms of vaccination except perhaps in the period immediately following vaccination when antibody levels are high. Under these circumstances the nasal secretions might reflect the high humoral antibody level. Then, again, when the cells are capable of putting up an adequate local resistance so that infection is

confined more or less to the surface, the impact upon the immunological mechanism may be minimal. This may sometimes explain the isolation of a virus from a sick patient with a failure to demonstrate a rising titre of antibody. It might also be one of the reasons why the child who is hypogammaglobulinemic does not succumb to its first assault from the common cold and indeed may recover successfully from a variety of viral assaults. The fact that such a child is a poor producer of antibody might be almost irrelevant in dealing with local infection provided cell response was good.

Another aspect of local infection is the "expendability" of the cells in different situations. Thus, when the cells mainly affected by virus invasion are in the upper respiratory tract the capacity to replace them might be more efficient than when an equal amount of damage occurs at a lower level. Perhaps of over-riding importance in dictating ultimate severity may be the mere coincidence of the type of bacterium which is present in the upper respiratory tract when virus damage is begun. When the flora is relatively non-pathogenic the normal forces of resistance may be sufficient, whereas an invasive pathogen quickly takes advantage of the local rupture in the defences. In infancy and early childhood the mere presence of edematous mucosal cells and profuse secretions may be very important in encouraging serious lung infection.

(b) *Systemic Virus Infection*

There is no doubt that some viruses reach the respiratory mucosa by way of the blood stream as a secondary occurrence (Fig. 2). This must be the course of events in such specific infections as measles, rubella, or smallpox. That systemic dissemination of virus occurs is supported by other clinical signs of visceral involvement such as the enlarged lymph nodes in measles.

It is hard to understand how virus enters the body at the time of primary exposure to infection without apparent involvement of respiratory cells. The focus of primary entrance of virus at the time of exposure, however, may not be the respiratory mucosa; the suggestion that the conjunctiva acts as an entrant point has been made and, if correct, could explain this paradox. It is a feature of infections of this type that they have a relatively long incubation period and during this time virus infecting particles must multiply in cells of such organs as the spleen, liver and lymph nodes prior to their secondary release into the blood stream.

When this secondary viremia occurs at the onset of illness, infection of respiratory cells will be more widespread and one might expect deeper interstitial cells also to suffer. In such systemic infections the actual dose of virus received by the individual on exposure may be of less importance in deciding whether he becomes diseased or not, for in the highly susceptible individual the build-up of virus within the body cells during the incubation period is probably more important. This may explain the seeming ease with which the susceptible person can acquire some of these systemic infections on slight exposure.

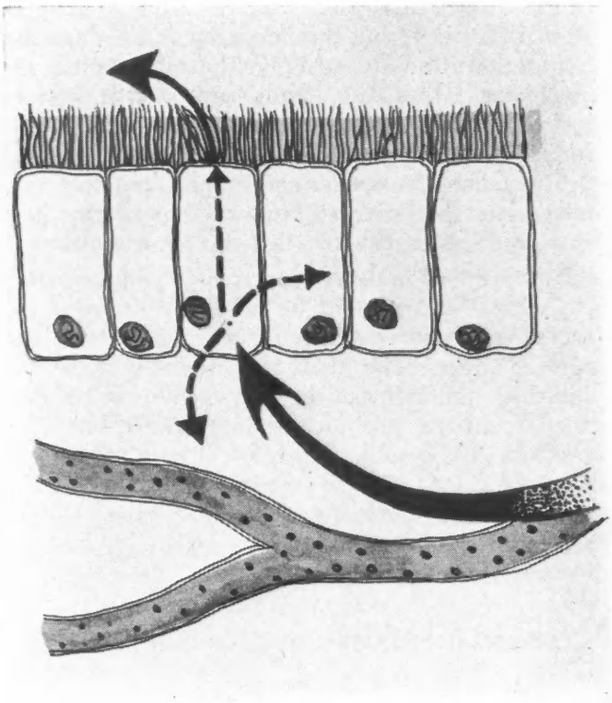

Fig. 2.—Systemic infection.

Virus infections which show this form of pathogenesis will have a main distinguishing feature. Recovery should always be accompanied by a sharp rise in humoral antibody. This, and maybe the more widespread assault on his cells, will render the individual more or less permanently immune; second attacks of such infections will be uncommon. As a natural corollary, it would follow that a method of vaccination which makes a sufficient impact on the immunity mechanism could be expected to give a solid protection.

Because of the fact that the use of antibiotics suppresses or prevents extensive bacterial superinfection, one is now in a better position to evaluate the damage produced by virus alone. These views of the pathogenesis of respiratory virus infection are supported by the histological picture observed. In a condition such as laryngotracheobronchitis it is sometimes possible to see lesions at what must be assumed to be an early stage. The brunt of the assault is then seen to be borne by the mucosa in which the earliest lesion is intense edema. This may indeed go on to an extensive mucosal desquamation and even submucosal ulceration, but it is often a striking feature that there is little evidence at an early stage of inflammatory reaction in the underlying tissues. In such cases histological changes are confined to the respiratory tract.

In contrast to this, the histology of measles is more diffuse and the respiratory tract is only one

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of the tissues in which signs of damage may be seen. Indeed, during the late stages of the incubation period the Warthin-Finkeldy cells may be seen in spleen, lymphatic glands and intestinal tract, indicating that cellular irritation has proceeded in widespread fashion. This is also a feature of the virus pneumonia seen in chickenpox, and the presence of intracellular inclusions deep in the lung tissue implies a systemic dissemination of virus.

It would, of course, be wrong to suggest that a complete case should be made by drawing too sweeping conclusions from a survey of a few histological pictures. The point is sufficiently made if it underlines the fact that the pathogenesis of respiratory infection is still unclear and indeed that even members of the same family of viruses may reach the respiratory tract by different routes. It is sufficient that we should appreciate that, in producing their effects, viruses may have reached their site of attack in more than one way.

II. Some Remaining Problems

(a) *Age and Virus Infection*

In the past the severity of pneumonia—especially of lobar pneumonia in the adult—was such that it demanded and received a great deal of study. With the introduction of chemotherapy, however, pneumonia is no longer such a serious problem, especially between the age of five years and about 40-45 years. The importance of pneumonia in the adult has, therefore, lessened and it becomes clear that the core of the problem of acute respiratory infection nowadays lies in the infant and young child. Pneumonia may be regarded as a good reflection of the severity of respiratory infection, for it might not stretch the facts too far to suggest that, particularly in the young child, a primary virus infection plays a dominant role in the development of all pneumonia. It is, therefore, instructive to examine some of the pneumonia statistics for Glasgow. The first table shows the notifications

TABLE I.—Age and Percentage Distribution of Notifications of Pneumonia in Glasgow, 1959

Age in years	*Notifications*	*Per cent*
Less than 1	695	15.5
" " 5	754	16.9
" " 45	973	21.8
" " 65	963	21.5
65+	1084	24.3
All ages	4469	100.0

by age for 1959. When the figures are depicted in this shortened age-distribution it is easy to be misled into under-rating the magnitude of the figures for the first five years of life. But the total of 1449 notifications in this group is nearly one-third of the total and far exceeds any other age-group; for it must be appreciated that the other age-groups cover four to eight times as many years of life.

This may be looked at in another way (Table II) by examining the proportion of deaths from all causes which are due to respiratory infection. The figures (again for Glasgow) are the combined deaths ascribed to acute respiratory infection and include pneumonia, influenza and bronchitis. The inclusion of bronchitis does not seriously invalidate the argument for, in the first year of life especially, it is often difficult to know when bronchitis shades into pneumonia. Clearly there is a remaining problem here, especially having regard to the likelihood that death measures only one aspect of the question. There seems more than a possibility that some of those who recover are left with continuing disabilities which produce chronic illness in later life.

TABLE II.—Proportion of Deaths from all Causes Due to Respiratory Infection—Glasgow, 1959

Age (years)	*Deaths from all causes*	*Deaths from respiratory infections (excluding tuberculosis)*	*Per cent*
Less than 1	799	86	11
" " 5	117	23	20
" " 45	809	41	5
" " 65	3822	469	12
65+	7989	1031	13
All ages	13,536	1650	12

It is not difficult to attribute possible reasons for this prominence of respiratory infection in childhood. Immaturity is apparent in a number of ways. The respiratory tract itself is imperfectly developed, so that the minor infection which would give the adult a few days of discomfort can produce a profound disturbance in the child. The inflammatory edema and excess of secretions can reduce the patency of the respiratory airway in such a way as to threaten life. This is well exemplified by a condition such as non-diphtheritic "croup" or laryngotracheobronchitis. Although this condition is common enough in the first few years of life, once the age of five is reached the anatomy of the larynx and trachea is sufficiently mature to permit edema to occur without producing life-threatening obstruction. One may also argue that in these first encounters with virus, the cells show a poor capacity to defend themselves. Finally, temperature response is less effective, so that minor but sudden climatic changes must be serious hazards. It is possible that it is not so much a question of the severity of the climate as the occurrence of sudden changes in temperature and humidity.

Another and contrasting aspect of age and respiratory virus infection may be worth consideration. Mumps perhaps would not strictly be regarded as a respiratory tract infection, but it serves as an obvious example of a virus infection which displays a relative simplicity when acquired in childhood, whereas in the adult the course can be severe and debilitating. In mumps it is easy to assume that this increasing seriousness with age is largely a

question of the cellular activity of testes or ovary. But evidence accumulates that other virus infections produce in the adult a more florid response than in the child. In the past, for example, pneumonia was not considered to occupy an important place among the complications of chickenpox, but in recent years an increasing number of cases of severe chickenpox in adults, often complicated by pneumonia, has been reported. It is true that a high proportion of these cases have been receiving corticosteroids or radiation treatment, but this is not invariable. I have myself seen three deaths from chickenpox in the past year, although in my first 20 years I saw only one such case. Another virus infection which may be increasing in importance in the adult is herpes simplex. When first studied it was shown that primary infection in the young child was common, was often asymptomatic, and seldom produced a severe illness. But one suspects that not only is one seeing in the older child and in the adult an increased number of manifest infections but that evidence of disseminated infection with widespread skin lesions or central nervous system involvement is occurring more frequently. To take a more recent experience with type 8 adenovirus and its responsibility for "shipyard eye" or epidemic kerato-conjunctivitis, a large outbreak occurred in some of the shipbuilding establishments in Glasgow in the period from November 1955 to October 1956, and it was an interesting observation that, although the severity of the lesion in the adult was sometimes considerable, we were unable to trace extension of infection to child family contacts.

Is there here some parallel with the behaviour of the poliovirus? Acquisition of this virus infection has, in the past 20 to 30 years, been delayed more and more into the older age groups, so that whereas in the 1920's the proportion of patients over 15 years of age was small, during the intervening period it has slowly risen. This has occurred especially in countries with high social and hygienic standards, and although one would be sure that improved standards of hygiene would be more effective in reducing the amount of infection from fecal contamination, it seems at least possible that some of the respiratory viruses, perhaps especially those of systemic origin, might show a similar change in age distribution. Again like poliomyelitis, this might occasion an altered reaction in the host—perhaps in the direction of increased severity.

(b) Treatment

The severity of many of the virus infections of the respiratory tract is probably related more to the coincidental presence, or to the immediate acquisition, of a pathogenic bacterium than to the toxic effects of the virus itself. There is now a considerable amount of controlled evidence to support the use of a broad-spectrum antibiotic as an important form of therapy even in conditions such as the common cold. This is more applicable to cases seen in general practice, and might have especial importance in infancy. In closed communities, such as residential nurseries or convalescent children's homes, it would be wiser to avoid such a method of treatment because of the greater risk of developing a local strain of staphylococcus of resistant pattern. No chemotherapy of proven value is yet available for the subjection of the virus element. This is unfortunate, for there is no doubt that, in virus influenza especially, fulminant cases are encountered where death occurs with such rapidity that it seems unlikely that bacteria play a dominant part.

(c) Prevention

The prevention of infectious disease—we often use, indeed, the term "eradication of an infectious disease"—is an approved principle of medical practice—so much approved in fact that we scarcely stop to examine either its desirability or its possibility of attainment. It is true that when prevention can be attained by the introduction of social measures which can be permanently maintained, then we may achieve not merely prevention but virtual eradication. We are so separated from contact that infection becomes a remote risk. This is the case, of course, in modern communities so far as diseases such as cholera or typhoid are concerned. But control of the air is a more complex problem than the control of water and sewage.

The success of artificial immunization in controlling smallpox and diphtheria has perhaps made our minds too ready to accept the view that some form of vaccination is the natural method to adopt as a preventive measure. However, it might well be stated as a principle of preventive medicine that artificial immunization should be adopted only when it is clear that all other methods of control have failed.

There would be general agreement that vaccination against smallpox and toxoid immunization against diphtheria are two of the most effective preventive instruments. Examination of their success may permit us to enunciate certain "factors which make a disease controllable by artificial immunization".

The following suggest themselves:

(a) The infection must be sufficiently severe and widely prevalent to induce public awareness and ensure that appeals to undergo vaccination will be successful.

(b) Prevention by the application of improved measures of social hygiene should be impracticable.

(c) The disease must be readily and accurately diagnosed. If several different diseases have similar symptoms and signs the public may feel that vaccination against one of them has failed.

(d) The method whereby the pathogen produces the disease process must be understood.

(e) The infecting agent must likewise be singular and stable. Multiplicity of serological types or a capacity to mutate may make an efficient immunizing agent difficult to manufacture.

(f) The immunizing agent must be safe and easy to prepare and use.

(g) The immunity produced must be potent and of reasonable duration.

Measured against these factors it seems that vaccination against some of the respiratory infections due to viruses is unlikely to prove a rewarding exercise. At present we regard influenza as the most severe and there is good evidence to support the argument that vaccination can, under certain circumstances, reduce the chance of infection. It must be admitted, however, that the responses to immunization campaigns have not been very satisfactory. And, it must be added that although vaccination may appeal to certain special population groups—for example, the well-educated and health conscious—it may be very difficult to apply to that section of the community which is particularly at risk—the children of those who are in lower-income groups and who are often difficult to educate in health matters. Vaccination may perhaps constitute a "second-best" which is to be used when nothing else is available. But it may be argued with some cogency that, if local virus implantation constitutes a large volume of the total respiratory infection, vaccination will prove a poor preventive. Capital expenditure might be more profitably applied to an intensive effort towards the discovery and testing of anti-viral agents, for it might prove more practical to permit infection to occur provided an interfering agent were available to limit spread. It is for this reason that one looks forward with great hope to the solution of the problems of the manufacture and administration of "interferon", for in this and perhaps in certain chemical substances may lie a solution of greater relevance than a vaccine. We already have in our possession the capacity to deal with any secondary bacterial effects, and actual experience of some virus infections may be an essential element in growth—something that should be acquired during a viral "safe period" in childhood and not delayed until the reaction becomes too florid.

SUMMARY AND CONCLUSIONS

A very large number of viruses are now known to produce respiratory illness, and it seems certain that the existing list is far from complete. The symptoms and signs produced by cellular damage to the respiratory tract fall within a rather limited range so that simple observation of the clinical picture must be of little help to the clinician in suggesting an etiological diagnosis. Many of these virus agents reach the respiratory tract by local implantation so that interference with cell metabolism is rapidly achieved without the mediation of the humoral immunity mechanisms. Influenza, the common cold and some adenovirus infections almost certainly achieve their effects in this way. In other virus infections, of which measles is a good example, the virus reaches the respiratory tract by means of the blood stream. Notable characteristics of these infections are the rather lengthy incubation period and the acquisition, after recovery, of a more or less permanent immunity.

There is a risk that we may too easily accept the view that the best method of dealing with the problem of virus infections of the respiratory tract lies in the production of virus vaccines. But the very multiplicity of the viruses involved must make us question such an approach. And, if local implantation of virus is the commonest method of infection it would seem likely that the possession of humoral antibody will not constitute an efficient defence.

Bronchitis and pneumonia remain as principal causes of death and continued ill health in infancy and childhood. Although a primary virus infection is the originating factor in the majority of these cases, it may be unwise to look to the discovery of new methods of active immunization as a practicable method of tackling this problem. The prosecution of studies aimed at enhancing local resistance to virus infection by chemical or other means, combined with the already existing antibiotics to deal with secondary bacterial invaders, should provide a more fruitful approach.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

A university faculty of medicine is not a trade guild of craftsmen and apprentices; it is not composed of initiates and novices aspiring to that rank. We are a body of men and women come together to learn and to co-operate in the endeavour to learn the answer to questions that are only partially solved, questions which may be some of them completely solved before the period of our association is ended, or possibly later in our lifetime, but possibly not until long after our places in this world have been taken by others. But whenever the solution may come, we may now and here help to bring that time nearer. We are, or should be, all helping each in his degree; those with greater experience helping those with less, but these latter also helping in spite of their inexperience. A certain professor at a certain university was once asked whether he knew anything about a certain subject and said, "No, I have not even lectured on it." Nothing helps so much as having to expound, that is, to expose one's ignorance of a subject. Nothing helps so much as to be asked pertinent questions to which we cannot give the answer. The greatest of Greek philosophers said that the fount and source of philosophy is wonder. What he meant was this: a dull, insensate man can go through the world and see nothing in it that is worth five minutes' consecutive thought; a man with a human intelligence sees on all sides that which creates in him a passion for understanding; and so long as his life is guided by this passion he is what the Greeks originally meant when they spoke of a man as a philosopher. At the age at which we enter a university we nearly all of us feel this passion, or, if we do not, what is a university for, but to awaken some measure of it in us?—J. B. Leathes: Inaugural Address delivered before the Faculty of Medicine in the University of Toronto, October 3, 1911; *Canad. M. A. J.*, 1: 1115, 1911.

SHORT COMMUNICATIONS

PERORAL JEJUNAL BIOPSY*

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THE PRESENT methods of peroral jejunal biopsy were derived from Wood's gastric suction biopsy tube which, because it was somewhat inflexible, was modified by Shiner into a more flexible model that would pass the pylorus and allow biopsy of the duodenal or jejunal mucosa.[1, 2] The series of biopsies reported here were obtained with a modification of the Shiner tube as devised by Rubin, the so-called "multipurpose" tube.[3] As its name implies, this tube can be used to obtain biopsies from the esophagus, stomach, duodenum, jejunum, rectum or colon. The principle of all suction biopsy tubes is that a knuckle of mucosa is sucked into an opening in the side of the capsule and cut off with a knife, in this model activated by a wire from the proximal or oral end. The distal end of the multipurpose tube is illustrated in Fig. 1. The tube with a bag of mercury tied to the capsule is passed by mouth into the stomach where it is allowed to pass down the small bowel to the desired level as seen in the plain radiographic film of the abdomen illustrated in Fig. 2. When it has reached this level the biopsy specimen, if taken, is retained in the capsule, and the tube is lifted to a higher level where another biopsy can be secured. Two or three such biopsies may be obtained before the tube is withdrawn. The biopsy specimen is a small button of tissue 2 to 3 mm. in diameter. A photomicrograph of a normal jejunal biopsy obtained by this method is illustrated in Fig. 3.

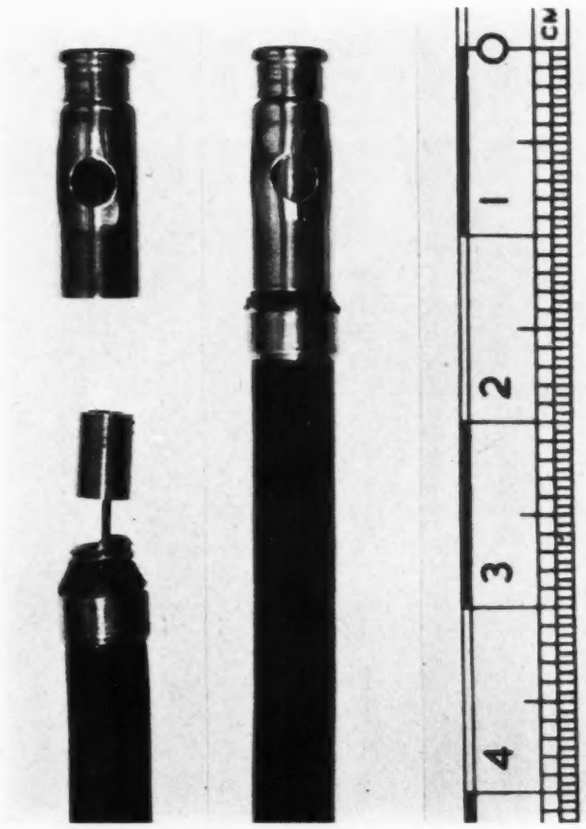

Fig. 1.—Distal end of multipurpose suction biopsy tube. Left view shows the capsule detached with a view of the cutting knife.

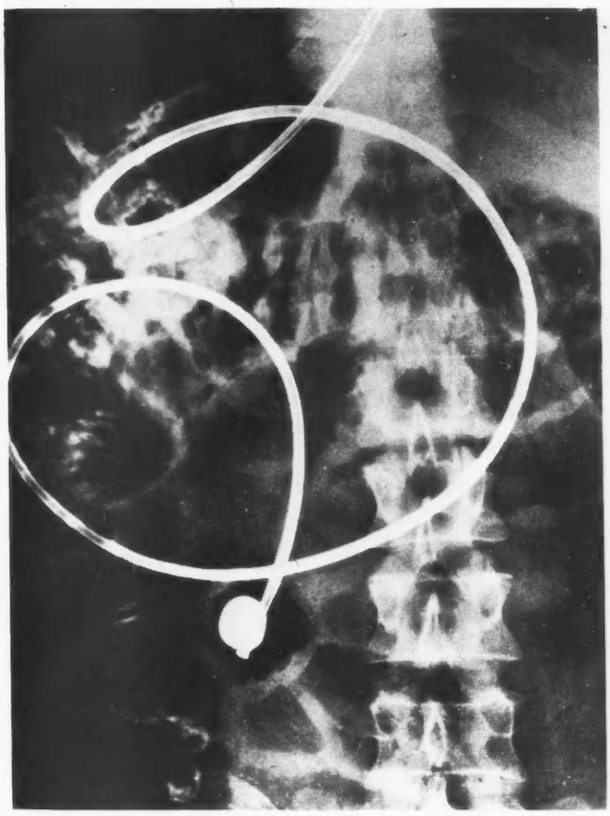

Fig. 2.—Postero-anterior view of suction biopsy tube in position.

Another widely used instrument for obtaining such biopsies is the Crosby capsule. In this instrument the knife is spring-activated and is cocked before the tube is swallowed and released by the suction which carries the mucosa into the port in the side of the capsule.[4] The capsule is attached to a thin polyethylene tube through which the suction may be applied. This system is similar to the multipurpose tube but allows the procurement of only one biopsy at a time. The limited number of biopsies obtained with each passage of these devices is a disadvantage. Attempts have been made recently to design biopsy tubes which return each biopsy specimen to the exterior via a hydrostatic system within the tube, thus allowing an indefinite number

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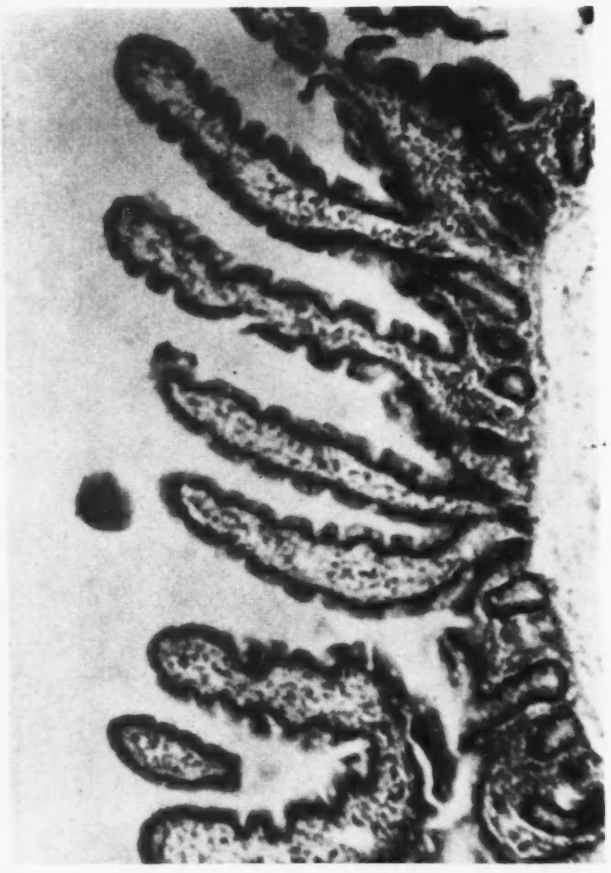

Fig. 3.—Normal jejunal biopsy.

of biopsies to be obtained with a single passage of the instrument.[5, 6] These tubes are not yet widely available, but the advantage of taking multiple biopsies at various levels in the jejunum and ileum is obvious.

In the past three years at this centre 62 peroral jejunal biopsies have been obtained from both adults and children with a variety of conditions but chiefly from patients with celiac disease. The multipurpose tube will consistently obtain a biopsy specimen, and we have failed to do so only once when the tube was in position. There may be some difficulty in passing the tube through the pylorus by means of positioning. On four occasions we have failed to secure a biopsy for this reason, and in three of these patients marked gastric dilatation was present. In our hands it has taken 1-2½ hours to carry out the biopsy procedure, which is somewhat longer than the time reported by others. Most of the delay in passage of the tube occurs at the pylorus, for once the mercury bolus is in the jejunum, onward passage is rapid. On three occasions we have biopsied duodenum rather than jejunum. No adverse effects from this procedure have been noted, but tests of stool for occult blood have not been done on all patients after the first few were negative. The only pre-biopsy precaution found necessary here is to ensure that the prothrombin time is normal.

TABLE I.—PERORAL JEJUNAL BIOPSY

Celiac disease	
Untreated	21
Treated	15
Others	
Normal	2
Diarrhea + weight loss	7
Iron deficiency anemia	2
Hypoalbuminemia	1
Diabetic steatorrhea	1
Resection steatorrhea	2
Postgastrectomy	4
Failed	5

As illustrated in Table I, 15 biopsies were performed on patients with celiac disease successfully treated for periods of six months to four years with a gluten-free diet. These patients were in clinical remission, and despite the absence of symptoms or biochemical abnormalities the biopsies in all of these patients were abnormal. Owing to the variability of the clinical presentation and the variety of absorptive defects, the diagnosis of untreated celiac disease may be difficult without the use of jejunal biopsy. In 6 of 21 untreated celiac patients we consider that the diagnosis could not have been established without jejunal biopsy; in 5 of the 21 cases this diagnosis, which had been doubtful, was established; and in 10 of the 21 the biopsy confirmed a diagnosis already reasonably well established from clinical and laboratory evidence.

Peroral jejunal biopsy has been of most value in the diagnosis and management of patients with

Fig. 4.—Jejunal biopsy in adult celiac disease. Note flattening of villi and cellular infiltration of the submucosa.

celiac disease, for in our experience the atrophic mucosa, as seen in Fig. 4, is specific for celiac disease and is an indication of gluten sensitivity. Furthermore, all patients with an abnormal atrophic mucosa have responded to a gluten-free diet. Therefore an abnormal biopsy is an indication for prescribing a gluten-free diet for the patient, and conversely, if the biopsy is normal such a diet is usually not advised.

In most instances there has been no great difficulty in the interpretation of the microscopic sections, but in a few cases with minimal changes and tangential cuts of the specimen it has been difficult to decide whether any abnormality is present. We have inspected the biopsies only and have not attempted evaluation of the total mucosal area as described by Rubin.[7]

In the case of several patients with disorders characterized by steatorrhea, such as diabetic diarrhea, protein-losing enteropathy, or gastric and small bowel resections, a negative biopsy was of value in eliminating the possibility that celiac disease (as a probable cause of the steatorrhea) was associated with these conditions. Since in celiac disease steatorrhea may be minimal or intermittently absent, the finding of a negative biopsy was helpful in children and adults with diarrhea, weight loss and anemia, but with normal or slightly increased fecal fat. In two patients with diarrhea, weight loss and a deficiency pattern on small bowel follow-through a normal biopsy was obtained; this finding eliminated diffuse small bowel mucosal disease as the cause of these abnormalities. In one of these patients the abnormal small bowel pattern later returned to normal, being apparently functional in nature; and in the other, minimal evidence of ulcerative colitis was found.

A summary of the uses of peroral jejunal biopsy is depicted in Table II. Firstly, this procedure is useful in the diagnosis of diffuse small bowel disease. We have not had the opportunity to diagnose regional enteritis, intestinal lipodystrophy, or intestinal lymphomata but the diagnosis of these conditions is possible by peroral jejunal biopsy. Salt *et al.*[8] recently described abnormal jejunal epithelium characterized by stunted villi and tall, clear, foamy epithelial cells with no inflammatory exudate in a syndrome characterized by very low levels of serum beta lipoprotein, acanthocytosis, and steatorrhea. Perhaps in time other obscure syndromes, especially those associated with absorptive defects, will prove to be associated with significant changes in the jejunal epithelium.

Secondly, such biopsies are of value in the diagnosis of obscure metabolic or nutritional disease; for example they may assist in differentiation between pancreatic and intestinal steatorrhea. In patients with osteomalacia who have iron deficiency anemia, hypoprothrombinemia or hypoalbuminemia as the sole or most marked manifestation of an accompanying celiac disease, the biopsy has been of great diagnostic value.

TABLE II.—USES OF PERORAL JEJUNAL BIOPSY

A. Diagnosis of diffuse small bowel disease
   (1) Celiac disease
   (2) Regional enteritis
   (3) Intestinal lipodystrophy
   (4) Lymphoma
   (5) Scleroderma
   (6) Diffuse carcinoma

B. Etiologic diagnosis in obscure disease
   (1) Steatorrhea—pancreas vs. small bowel
   (2) Osteomalacia
   (3) Iron deficiency anemia
   (4) Hypoprothrombinemia
   (5) Hypoalbuminemia
   (6) Diarrhea with abnormal small bowel pattern
   (7) Postgastrectomy steatorrhea

C. Prognosis for gluten-free diet in celiac disease

D. Research
   (1) Study of small bowel epithelial function
   (2) Study of celiac disease
      —nature of the disease
      —changes with gluten-free diet

Thirdly, as already noted, those individuals with celiac disease and the characteristic microscopic changes have been found to respond very satisfactorily to a gluten-free diet.

Fourthly, the peroral jejunal biopsy is of value in investigative studies of the small bowel epithelium. In this respect, electron microscopy and histochemical studies of the jejunal epithelium, in particular, are enlarging our knowledge of its normal structure and function.[9] It is hoped that the use of peroral jejunal biopsy will be helpful in further elucidating the nature of celiac disease. We are particularly interested in determining whether the abnormal mucosa returns to normal with the clinical remission induced by a gluten-free diet. In the five patients thus far biopsied after a variable period of treatment, there has been no apparent change in the appearance of the proximal jejunal epithelium. It may be that, as suggested by Rubin,[10] the upper jejunum is the last segment of gut to return to normal because with treatment the lesion recedes proximally from the ileocecal valve.

SUMMARY

Peroral jejunal biopsy is a relatively simple and completely safe procedure which has been of most value in the accurate diagnosis of lesions which cause diffuse changes in the intestinal epithelium and which may present clinically with a variety of absorptive defects.

REFERENCES

1. WOOD, I. J. *et al.*: *Lancet*, **1**: 18, 1949.
2. SHINER, M.: *Gastroenterology*, **33**: 64, 1957.
3. BRANDBORG, L. L., RUBIN, C. E. AND QUINTON, W. E.: *Ibid.*, **37**: 1, 1959.
4. CROSBY, W. H. AND KUGLER, H. W.: *Am. J. Digest. Dis.*, **2**: 236, 1957.
5. BAKER, S. J. AND HUGHES, A.: *Lancet*, **2**: 686, 1960.
6. FLICK, A. L., QUINTON, W. E. AND RUBIN, C. E.: *Gastroenterology*, **40**: 120, 1961.
7. RUBIN, C. E. *et al.*: *Ibid.*, **38**: 28, 1960.
8. SALT, H. B. *et al.*: *Lancet*, **2**: 325, 1960.
9. PADYKULA, H. A. *et al.*: *Gastroenterology*, **40**: 735, 1961.
10. RUBIN, C. E.: *Ibid.*, **39**: 260, 1960.

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A CLINICAL STUDY OF METHAQUALONE: A NEW NON-BARBITURATE HYPNOTIC

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THAT increasingly large numbers of people seek the aid and solace of central nervous system depressant drugs to enable them to cope with the trials and stresses of modern-day living must be accepted as an unpalatable fact. Physicians are faced with the problem of meeting this situation, and apparently do so by prescribing literally tons of barbiturates, other sedatives and tranquillizing drugs. Patients most frequently request "something to help me fall asleep", and for this purpose the mainstay has been the administration of one or other of the barbituric acid derivatives. These are certainly effective, but it is becoming quite apparent that they are not entirely innocuous. Habituation, accidental overdosage,[1] excitation rather than depression in the young and the very old,[2] and other less common serious untoward effects have led to legislation to restrict the freedom with which these drugs may be obtained. It is not surprising, therefore, that there should be intensive investigation directed to the re-evaluation of older preparations and of new drugs which may have less potentiality for harm. Chloral hydrate and paraldehyde are examples of older drugs which have been resurrected. These, however, present problems of taste and odour which make them unacceptable to most patients. Glutethimide and methylpyrolon are examples of non-barbituric acid derivatives which have recently been introduced.

The present study is concerned with an evaluation of a new non-barbiturate hypnotic, methaqualone (2-methyl-3-o-tolyl-4-quinazolone hydrochloride). Gujral *et al.*[3-6] called attention to the hypnotic properties of a series of quinazolone derivatives. The most promising of these was methaqualone, which has the following structural formula:

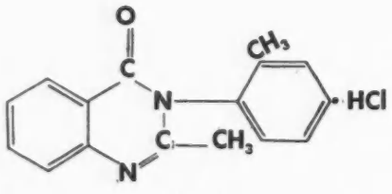

Fig. 1

Boissier, Dumont and Malen[7] carried out an extensive pharmacological investigation of this compound and concluded, in agreement with Gujral, Saxena and Tiwari,[4] that this compound possessed good hypnotic activity. It has low toxicity with a very favourable therapeutic index; 4 as compared with 2.5 for phenobarbital. Induction is rapid and sleep is not preceded by any stage of excitement or motor incoordination; recovery is smooth and calm. The drug strongly antagonizes the convulsive effects of pentylenetetrazol, but has little effect on the convulsive effects of strychnine or picrotoxin, indicating that its effects are on the cortex, with minor or no effect on the bulbar region or spinal cord. The drug definitely reduces the intensity of the action of central nervous system stimulants such as amphetamine, piperadol and caffeine. Methaqualone and the following drugs: chlorpromazine, pethidine, opiates, and dextromoramide, are mutually potentiating when administered together.

In chronic toxicity studies in rats and dogs, long-term feeding with doses of 40 to 50 mg. per kg. daily for five days per week for three to five weeks showed no evidence of toxicity. Growth, blood picture, and renal function were unimpaired. In a later study Boissier and Font du Picard[7a] demonstrated that methaqualone potentiates the analgesic action of codeine.

With this favourable pharmacological background, Ravina[8] undertook a clinical evaluation of methaqualone. One hundred patients were given the drug in a dose of 150 mg. orally or 200 mg. as a rectal suppository. Sleep occurred rapidly, usually within 10 to 20 minutes, and induction was not preceded by motor or psychic excitement. Sleep lasted for six to eight hours, and on awakening the patients were immediately alert and free from headache, dullness or dizziness, which so often follows the administration of barbiturates. Of the 100 patients studied, the results were qualified as excellent to good in 54%, moderately good in 28%, mediocre in 12%, and as failure in 6%. Of the six failures, five were seriously ill patients in constant pain who had not responded to many other hypnotics.

Parsons and Thomson[9] carried out a double-blind study comparing methaqualone at two-dose levels, namely 150 mg. and 200 mg., cyclobarbitone 150 mg. and 200 mg., and a placebo. The conclusion from this investigation was that methaqualone is a reliable hypnotic, and no important difference could be detected between the hypnotic action of 150 mg. methaqualone and 200 mg. of cyclobarbitone.

The present investigation was undertaken to extend these studies.

METHOD

The double-blind technique was used. Identically appearing capsules were prepared containing either 150 mg. of methaqualone,* 100 mg. of secobarbital, or lactose (placebo). The letters A, B or C were the only identifying marks on the label; and physicians, nurses and patients were unaware of which bottles contained the active ingredients or placebo.

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*Supplied by Charles E. Frosst & Co., under the trade name "Mequelon".

One hundred and five hospitalized patients (51 males and 54 females) in the public wards were the subjects for this study. The average age of the entire group was 45 years (range 14 to 81). The only criterion for selection was that they had been receiving a hypnotic to aid them to sleep for some time. In order to avoid error, all patients in the group received the same preparation one-half hour before retiring. The preparation administered was changed every five days. All three preparations were received by 28 patients; 40 received two preparations, and 37 received only one.

At the end of the study the code was broken and it was found that preparation A, the placebo, was dispensed 303 times; preparation B, methaqualone, 332 times; and preparation C, secobarbital, 310 times. The same observer classified all the results, awarding a poor, fair or excellent mark based on promptness of induction, duration and quality of sleep, number of awakenings during the night, and the general condition of the patient in the morning.

RESULTS

There was a significant statistical difference between the results achieved by the placebo and by the hypnotics. The chi square value, calculated from the data in Table I, is 162; the probability of chi square on the 0.001 scale is 18.5.[10]

TABLE I.

Medication	*Results*			
	Mediocre	*Good*	*Excellent*	*Total*
Placebo (A).....	82	104	117	303
Methaqualone (B)..	23	63	246	332
Secobarbital (C)...	9	48	253	310
Total.....	114	215	616	945

Thirty-eight per cent of the patients receiving the placebo slept well as compared with 74% excellent results for methaqualone and 81% for secobarbital. Of 114 poor results, 72% followed the placebo, 20% methaqualone, and 8% secobarbital.

It should be noted that 15% of the patients were receiving tranquillizers, but since these were fairly evenly distributed among the three series, no account of this was taken in assessing the results. The hypnotic side effects such as fatigue, drowsiness, heaviness and headache were observed in 35 instances. It is of interest that the majority of these, 40%, were reported by patients after the placebo, 37% after secobarbital, and 23% after methaqualone.

No noteworthy differences were observed between the effects of the two hypnotics as far as promptness of induction and duration of sleep were concerned.

Hepatic function studies were made in 15 patients at the end of treatment. All were within normal limits. Hematological studies were not carried out, since Bernard[11] had already shown that methaqualone produced no alterations in the blood picture.

SUMMARY

A brief review of the literature on the pharmacological and hypnotic effects of a new chemical compound, methaqualone, has been presented. A double-blind study comparing the hypnotic effects of 150 mg. of methaqualone, 100 mg. secobarbital and a placebo is reported.

Methaqualone proved to be an excellent night-time sedative in 74% of 332 administrations as compared with 81% of 310 secobarbital administrations and 38% of 303 placebo administrations.

No significant side effects were observed. In 35 patients in whom post-hypnotic fatigue, drowsiness, heaviness or headache occurred, 40% followed the placebo, 30% the secobarbital, and 23% the methaqualone. Methaqualone, a non-barbiturate hypnotic, appears to be a distinct contribution to the group of drugs useful for night-time sedation.

REFERENCES

1. GOODMAN, L. S. AND GILMAN, A.: The pharmacological basis of therapeutics, 2nd ed., The Macmillan Company, New York, 1955, p. 123.
2. BARE, W. W.: *Am. J. M. Sc.*, **241**: 766, 1961.
3. GUJRAL, M. L., KOHLI, R. P. AND SAXENA, P. N.: *J. A. Physicians India*, **2**: 29 (Med. 2, No. 3, Feb.), 1955.
4. GUJRAL, M. L., SAXENA, P. N. AND TIWARI, R. S.: *Indian J. M. Res.*, **43**: 637, 1955.
5. GUJRAL, M. L., KOHLI, R. P. AND SAXENA, P. N.: *Indian J. M. Sc.*, **10**: 871, 1956.
6. GUJRAL, M. L., KOHLI, R. P. AND TIWARI, R. S.: *Ibid.*, **10**: 877, 1956.
7. BOISSIER, J. R., DUMONT, C. AND MALEN, C.: *Thérapie*, **13**: 30, 1958.
7a. BOISSIER, J. R. AND FONT DU PICARD, Y.: *Ibid.*, **15**: 57, 1960.
8. RAVINA, A.: *Presse méd.*, **67**: 891, 1959.
9. PARSONS, T. W. AND THOMSON, T. J.: *Brit. M. J.*, **1**: 171, 1961.
10. FISHER, R. A.: Statistical methods for research workers. Vol. 1, 10th ed., Oliver & Boyd, Ltd., London, 1946.
11. BERNARD, J.: Report on tests for activity and harmlessness to hemopoietic organs. Private communication.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

It is evident that medicine has not lost its popularity as a profession in Ontario, and the classes in all the universities are as large, if not larger than ever; the University of Toronto leading with a first year class of one hundred and forty-four students: this too in spite of the raising of the matriculation standards.

The wonder is what is to become of these students when they graduate, and yet when the rapid growth of Canada is contemplated, it is evident that the supply will not be greater than the demand.

There is a feeling in university circles that in the near future the entrance standards must be raised still further, and it would not be surprising if in due course senior matriculation would be demanded.

When the newer provinces have established universities of their own, with properly equiped medical departments, it stands to reason that the eastern school will lose a marked number of students. More than ever then they must make their courses attractive to the best men if they are to flourish, and no doubt post-graduate work will also be developed as it has not been attempted in the past.—Editorial, *Canad. M. A. J.*, 1: 1206, 1911.

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CO-OPERATING WITH THE PRESS

IN the weeks following the appearance in this Journal of the editorial entitled "The Safety of Blood Transfusions" (*Canad. M. A. J.*, 85: 658, 1961), editorial writers of the public press devoted considerable space to comments upon it. A very few of these were adverse and deserve the close attention of the medical profession. This editorial was apparently interpreted by a well-known daily newspaper as a defence of parochial interests when it said "We are flattered, in a way, that the C.M.A. has approached the daily and weekly newspapers across the country to *bail them out* of the difficulty into which this article ('Three Blood Transfusions out of Four are More Likely to Harm Than to Heal') *has put them.*" (The italics are ours.) Plainly, the inference seems to be that if the availability of human blood for transfusion purposes is curtailed, only the medical profession (and specifically the professional organization, the C.M.A.) will suffer. This interpretation of the intent of our editorial is both revealing, if the writer was not being facetious, and disturbing.

The editorial "The Safety of Blood Transfusions" was written (a) to protest the unsupported denunciation of a vital medical service by a physician and (b) to place on record *for public information* the best information available. With regard to the latter purpose, at a time when the editorial was still in preparation, the *Ottawa Journal* (August 31, 1961) called for such information in these terms: "Where are we then?. . . . The layman is left not only in doubt but in anxiety. Blood transfusions . . . depend on public support. Is there not a responsibility here on the part of either the Government or The Canadian Medical Association to clarify a confusing and disturbing argument?"

Our editorial was, in effect, preaching to the converted (and many physicians wrote to tell us so), but our channel of communication with the non-professional reader is through news releases based on material appearing in the Journal. A subsequent news release from The Canadian Medical Association, dated September 11, 1961, contained only factual material that could be used by newspapers, if they wished, and in any form they saw fit. The remainder of the editorial was *not* directly transmitted to the public by this Journal or by The Canadian Medical Association.

The newspaper quoted in the opening paragraph of this editorial continued, "It [the medical profession] has a Code of Co-operation, for example, which it quotes to us as an awful warning of our responsibilities: 'On all matters of health and medical news, representatives of the news media should make every reasonable effort to obtain authentic information from qualified sources before proceeding to publish or broadcast. The news media should make every effort to seek out spokesmen designated by the local medical society.'"

It is hard to understand such objections to the Code of Co-operation because this statement of principles was drawn up by a group representing both the public press and organized medicine. Incidentally, the Code of Co-operation says far more about the duty of the physician to make himself available to the press than it says about the responsibilities of the press to the profession. It appears that the existence of this Code is unknown to more than a minority of the two large and influential bodies whose co-operation in providing reliable information to the public is so essential. Apparently much still needs to be done to make this pact of mutual assistance generally effective.

Many factors underlie the guarded attitude of the profession toward sporadic, independent and often hasty expressions of opinion by individual physicians. If The Canadian Medical Association, through its Code of Ethics, did not recommend this attitude it is probable that the profession would "invent" it, as Voltaire said of God. We have been given some salutary lessons by our opposite numbers in the public press, and some of them should be given wide currency among the profession.

Many, if not most, editors of newspapers and magazines make a strong distinction between their responsibilities to consult official sources on "stories" written on medical topics by journalists on the one hand, and articles submitted to them by individual physicians on the other hand. All of the safeguards The Canadian Medical Association wishes to see invoked are acknowledged in the first situation, *but* apparently no such obligation is admitted in the second. As a well-known editor said some time ago, "If one of my boys is writing on a medical subject we research the hell out of it. But if a doctor comes in and swears that the moon is made of green cheese or that he has found a cure for cancer in his flower bed, I'll print it." In other words, when a physician submits an article to the public press, regardless

of its fitness, its foundation in modern medical knowledge, or its potential for damage to public interest, it may be accepted for publication without further scrutiny. This alone should give pause to the physician who is tempted to become an oracle. He is held to bear the full responsibility for all the effects of publication. Many of these journalistic forays on medical subjects have a disturbing effect on the public. A columnist in the *Argus* (Stonewall, Manitoba) made the following very astute observation in his column, *The Passing Show*: "The average man is likely to be fast approaching the stage of not knowing whom or what to believe. So many firm-held beliefs on this and that are being riddled by 'experts' in so many fields. Particularly so in the field of medicine. Some weeks ago, one prominent physician published in a nationally circulated Canadian magazine a blast condemning blood transfusions—which he claimed could do far more harm than good and might transmit diseases instead of restoring health. He stated, flatly, that 'three out of every four blood transfusions are more likely to harm than to help'. The vast majority of the populace—including a great number of voluntary blood donors—'sold' on the belief that blood transfusions saved a great many lives—would have cause to wonder how much weight this medico's opinion carried. The layman must be excused if he is a bit confused. The above-mentioned statements by a prominent medico, widely circulated in the public prints, may be in the nature of 'minority reports'—but they are disturbing, nonetheless, and could have the effect of weakening the confidence of an average man in the skill and knowledge of his physician. Because he is apt to recall that a number of great discoveries and advances in this field came about through efforts of lone individuals who persevered in face of the ridicule and hostility of their colleagues. And he is further apt to get the notion in his noodle that it is not conducive to public confidence for medicos (or retired army generals) to argue about techniques and tactics in the public prints."

Finally, the individual physician might reflect that in many instances the press is unlikely to want his name and opinion on a subject that is straightforward and non-controversial; such subjects have little or no "news value". The warmer the welcome to speak out, the more caution he should exercise in *preparing* his remarks. There are several advantages in referring the press to experts through the chairmen of established public relations committees of the profession. The physician with special interest in and knowledge of a specific subject is able, without waste of time and effort, to produce a balanced authoritative statement that will contribute in a positive way to public information. The expert will be able to represent the many disciplines, within and outside the profession, that must be drawn upon for "the truth as we know it" in a contentious problem. Some segments of the press seem unaware of, or choose to ignore, the fact that most physicians are not expert in all aspects of medicine.

In brief, there are good reasons for handling public communications through professional channels; this is substantiated by the excellent results of liaison between public relations committees of the profession and the news media. However, this still leaves the problem of convincing the Canadian public and its newspapers, of our good faith and our overriding interest in public welfare, above all else. But here, as in so many other problems, the burden falls upon the shoulders of the individual physician as he communicates from day to day with his patients and members of the public or the Fourth Estate.

THE GAIRDNER AWARDS

THE third Annual Awards Dinner of The Gairdner Foundation was held at the Royal York Hotel, Toronto, on November 10, 1961. Created in 1957 through the generosity of Mr. James A. Gairdner, a former President of the Canadian Arthritis and Rheumatism Society, The Gairdner Foundation undertakes to reward achievement in the fields of research and treatment in the rheumatic diseases and in cardiology. Under the guidance of a distinguished medical board, the Foundation assembles men of science from any part of the world and presents to them, without reservation, awards of $5000 in acknowledgment of their contributions to medical science. At intervals of four years a special award of merit amounting to $25,000 may be made. All awards are made solely at the discretion of the Foundation and are not open to application on the part of potential candidates.

A magnificent dinner was held under the chairmanship of Professor K. J. R. Wightman and concluded with the presentation of illuminated scrolls and cheques by His Honour J. Keiller Mackay, Lieutenant-Governor of Ontario, to the following distinguished recipients of the Gairdner Awards for 1960: Sir Russell Brock, London, England; Professor Alan C. Burton, London, Ontario; Dr. Alexander B. Gutman, New York; Professor Jonas H. Kellgren, Manchester; and Professor U. S. von Euler, Stockholm.

The replies of the recipients were sprinkled with humour. Sir Russell said that he was reminded of the story of an eminent scientist who had received many honours and awards and who eventually concluded, on one of these occasions, that the statements made in each citation must indeed be true. Musing aloud on the way home he said to his wife, "I wonder how many great men there are in the world?" His wife replied quickly, "One less than you think, dear." He also recalled that, thirty years ago, when in the United States as a Rockefeller grantee he had been attracted to Toronto by the work and reputation of Dr. Robert Janes in the field

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of thoracic surgery. Advances contributed by such work had done much to set the stage for later workers in cardiac surgery. Sir Russell returned to Toronto again years later to review and discuss with Dr. W. G. Bigelow his pioneer studies in hypothermia.

In his turn, Professor Burton said that he felt unable to resist constructing a hypothesis which would explain why he, a biophysicist, was chosen for this award. The first element in his theory was that since feelings of nationalism play a major role nowadays, at least one Canadian had to be so honoured; secondly, there were only a few workers in the field of cardiovascular physiology in Canada and the choice was limited; and, thirdly, he noted that Dr. W. G. Bigelow of Toronto had been a recipient in a previous year, so it was clear that the judges were going through the alphabet! Dr. Burton also read a telegram from his laboratory staff and graduate students which said "Congratulations. In response to your instructions, we are hard at work on another one." The other recipients responded with brief but gracious expressions of thanks.

His Honour J. Keiller Mackay spoke briefly, praising the generosity and farsightedness of Mr. James A. Gairdner. In a forthright reply, Mr. Gairdner outlined the aims and hopes that inspired the creation of the Foundation; chief among these was his desire to bring the architects of medical progress in several fields together in Toronto so that they could engage in an informal exchange of views for the benefit of the physicians in the community. He expressed the hope that the Gairdner awards would make a material contribution to the development of the city of Toronto as a major centre for medical research.

The recipients were kept well-occupied during their few days in Toronto, visiting hospitals, conducting ward rounds and discussing their respective fields of interest informally. On November 11, under the chairmanship of Professor C. H. Best, they presented the Gairdner Foundation Lectures at the Toronto General Hospital. The lecturers had been informed in advance that the subject matter of their addresses would be entirely of their own choosing. This allowed the recipients a good deal of latitude and they were unable to decide whether to describe aspects of their own contributions or to deal with some other matter which they felt was of importance. The result—a variety—seemed to be immensely to the liking of the audience.

Professor von Euler, in a scholarly discourse, argued that it was important to tolerate and to reward all the varieties of scientists, not simply those working in the "conventional" ways; that some degree of heresy is necessary in the scientific community.

Professor Kellgren recounted the findings of epidemiologic studies which employed serological tests for the rheumatoid factor, serum cholesterol and uric acid determinations in a variety of populations who were also examined for clinical evidence of gout and rheumatoid arthritis. A number of unexpected and conflicting observations have been made, such as the variation in the "rheumatic complaint threshold" among various segments of the population, the marked disparity between clinical evidence of rheumatoid arthritis and the presence of a positive sheep cell agglutination test (SCAT), and the urban-rural difference between the distribution of positive SCAT tests. These and other riddles can be resolved only by the continuation of painstaking epidemiological investigations.

Dr. Gutman indicated that he believed the cause of gout is related to the absence of an enzyme or enzymes (an inborn error of metabolism) which play a role in the metabolism of amino acids. He stressed that despite recent major advances in the management of this disease, specifically in our ability to control the acute attacks and prevent the development of tophaceous gout, the cause of gout remains unknown. He challenged younger physicians to tackle these important and intriguing problems.

Professor Burton gave an impressive example of the application of physics to medical problems. His demonstration of the fundamental nature of the studies of Laplace (1821) and Robert Wood (1896), and their application to the clinical problem of the failing heart was stimulating and rewarding.

Sir Russell Brock concluded the Lectures with a description of his philosophy of surgery. It was evident that Sir Russell had searched his heart and his experience and out of these had produced a moving testament of service to a high and difficult ideal. His message will remain in the memory of his hearers long after other events have faded.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

"Illinois has just passed a bill abolishing the use of the public drinking-cup. Chicago, through its health department, supported by the newspapers, has waged an active campaign against it. The city bacteriologists have collected drinking-cups from various school buildings, hotels, railway stations, and stores in the city of Chicago, and have made microscopic examinations and bacterial cultures from these cups. The most frequent varieties of germs found are various pus germs, also, specimens of pneumonia and diphtheria bacilli have been found. Guinea-pigs have been inoculated with these cultures, and the results of these tests, according to the city bacteriologists, prove the deadly nature of these bacteria. All the pigs inoculated with the bacteria of the pus infections developed fatal abscesses. The tests with the diphtheria culture were also positive, as proved by the occurrence of the disease."—*The Journal of the American Medical Association*, quoted in *Canad. M. A. J.*, 1: 1161, 1911.

Letter to the Journal

THE BIOCHEMISTRY OF MENTAL DISEASE

To the Editor:

A short while ago an article called "The Biochemistry of Mental Disease" appeared in *The Canadian Medical Association Journal* (85: 487, 1961). The author discussed our adrenochrome hypothesis of schizophrenia briefly. While the references quoted are accurate in themselves, they are also misleading, for by omitting any account of the published support for this hypothesis a false impression results. It is important that readers should be told that not everyone agrees with our hypothesis, but they also have the right to know that many reputable scientists have supported it with articles published in scientific journals.

As our hypothesis stands now, we believe that the essential biochemical fault in schizophrenia is an abnormal diversion of adrenochrome into adrenolutin rather than into 5:6 dihydroxy-N-methyl indole. Adrenolutin, a trihydroxy indole, is psychotomimetic for animals and for man, whereas the dihydroxy indole is much less toxic.

The hypothesis as outlined leads to several subhypotheses, some of which were inferred by the reviewer. These are (1) that adrenochrome must be present in the body of schizophrenics. If adrenochrome is present it would prove that adrenolutin and 5:6 dihydroxyindole are also present, for these two compounds have been found to be formed from adrenochrome *in vivo*.[52] (2) Adrenochrome and adrenolutin are psychotomimetic, whereas the dihydroxy indole is not.

Dr. Sourkes referred to these issues and ascribed to us the following claims (1) that adrenochrome has a hallucinogenic action in man; (2) is present in plasma (we did not state in high concentration, because "high" is a value term—high compared to what?); (3) is formed at an abnormally high rate; (4) or is detoxified too slowly.

He stated that "all of these findings have now been questioned". We shall deal here with his main reference[51] and also with much evidence which he ignored. In fact, item one has been corroborated several times and item four is not in dispute; at least we can find no reference to it in a wide search of the literature.

We shall discuss the fourth item first. Hoffer[23] reported that when crystalline adrenochrome was given to patients by vein it was removed from the plasma more slowly in schizophrenic patients than in other diagnostic groups. The Payza and Mahon (1959) assay was used. This method has been questioned by Feldstein, but his criticism applied only to the question whether adrenochrome was naturally present in the body. He has stated publicly that the method worked well for analyzing adrenochrome in blood when it was added. Thus our claim that adrenochrome was removed more slowly from schizophrenic plasma was valid. To this time there has been no scientific report either denying or corroborating this claim.

Dr. Sourkes then attempts to deal with the question, "is adrenochrome hallucinogenic?" His main source of information here is a paper written by Smythies,[51] who stated "Hoffer's only experiment using such controls [he refers here to placebo, etc.] produced negative results." When this error appeared in the *Lancet*, we decided not to correct it because we expected other critics to re-read the original paper (Hoffer[22]).

Dr. Sourkes does not make it clear that he is referring to Smythies' interpretation of Hoffer's results and not to Hoffer's own conclusions. Smythies reassessed Hoffer's conclusions owing to a difference of opinion which has not been resolved. Hoffer concluded that it was possible to differentiate between adrenolutin and placebo in a double-blind experiment and that he had done so successfully. The disagreement arose in this manner. In 1956, when these experiments were carried out, the adrenolutin available was not entirely pure or stable, and consequently it deteriorated slowly. During the first half of the experiment when the adrenolutin was more yellow than green a clear differentiation was made in a double-blind study on 13 subjects. In the second half of the experiment, when the adrenolutin was more green than yellow (its normal colour, as its name suggests, is a golden yellow), the observers could not differentiate between drug and placebo.

We think that this was evidence of a previously active substance becoming inactive—as the colour change suggested. Smythies, for reasons which are still unclear to us, insisted that the subjects who had the active adrenolutin and those who had the deteriorated compound must be lumped together because it had been planned that way in the original design. We consider that this is a much too slavish attitude toward design.

At the time of the experiment the experimenters' reports on the subjects were recorded and the subjective account by the subjects was obtained. These became part of the data before the drug was decoded. These are the data which were summarized in this paper. If we now examine the first 14 subjects only as described in the original paper (the first seven received adrenolutin first, then placebo; the second in reverse order), for the presence of certain clinical changes, one will find that a certain group of changes occurred only in the subjects given adrenolutin and another set occurred only in those given placebo. The following categories of clinical changes are used. (1) *Perceptual changes.*—When subjects had dizziness, had hallucinations when stimulated by a stroboscope, had difficulty focusing visually, etc. (2) *Changes in thought.*—These included sluggishness in thinking, referential and paranoid thinking, difficulty in solving simple arithmetic problems, memory disturbance. It does not include statements by subjects that they had difficulty thinking. (3) *Changes in personality.*—These included becoming irritable, argumentative, or boastful, and developing inappropriate behaviour. (4) *Mood.*—This included only those subjects who became depressed. (5) *Carry-over next day.*—This included great fatigue, disinterest, dizziness or changes in personality.

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CLINICAL RESPONSE TO ADRENOLUTIN AND PLACEBO, FREQUENCY OF OCCURRENCE

	Adrenolutin		*Placebo*	
	First	*Last*	*Last*	*First*
Perception	4	4	—	—
Thought	3	3	—	—
Personality	4	2	—	—
Mood-depression	2	—	—	1
Carry-over	4	1	—	1
Total	17	10	0	2

It is obvious that far more changes occurred in those who took adrenolutin: 27 changes occurred in the drug group, only 2 in the placebo group. These changes were independent of the order of giving these drugs.

In marked contrast, seven of the placebo subjects had evident anxiety for the greater part of the experimental run. This did not occur with any of the adrenolutin subjects.

When Smythies wrote his review, he apparently no longer believed that adrenochrome produced psychological changes, for he quotes authors who have told him in personal communications that they could find no evidence for its activity in humans. But these authors have not published their results, so that we cannot know what sort of adrenochrome was used, to whom it was given and how its effects were evaluated. Smythies states that Schwarz *et al.*[49] "observed no psychological or behavioural effects". Schwarz and his colleagues, who did us the courtesy of telling us about their work before publishing it, considered that they had confirmed us. This is what they wrote:

"It was difficult to evaluate the effects of adrenochrome on the psyche. The epileptic appeared to be relaxed and became drowsy. One schizophrenic appeared to show loosening of associations and increase in disturbance of body image; for instance, he raised his hand, gazed at it and said, 'My arm wiggles and waves—ha, ha.' The other schizophrenic who received adrenochrome experienced cataplexy on two occasions which persisted for more than 30 minutes. At these times his upper extremities were held in unnatural positions that could not be maintained for long by volunteers who served as controls. This was not his usual reaction and a similar state did not develop with either mescaline or LSD-25."

Von Taubmann and Jantz[57] did not think that adrenochrome was the active substance. They did find activity in their adrenochrome preparation, but felt that it was due to some further oxidation product. It is, of course, also possible that pure mescaline may be inactive and that its activity is due to some degradation product, as Harley-Mason, Laird and Smythies[21] suggested.

Adrenochrome and adrenolutin have produced behavioural changes in animals as well as in man. Indeed no one now questions adrenochrome's activity in animals. We have reviewed the evidence in earlier reports. It was shown that adrenochrome was active in modifying behaviour of several species of animals. The drug was less effective in atomistic studies,[39] and became more effective the more natural the setting. Similarly, with more sophisticated conditioning trials the more effective was adrenochrome.

Kuchino[36] studied the catatonic-producing qualities of hallucinogens including adrenochrome. He states that adrenochrome, being an adrenaline metabolite which exists in the organism, is of greater interest as a catatonic-producing agent than artificial substances, because of its possible connection with the autotoxic theory of schizophrenia. He experimented with rats, dogs and monkeys. In doses of 0.1 mg. per 100 g. body weight adrenochrome produced catatonia in rats. In dogs and in monkeys smaller doses did not produce catatonic-like states, but they abolished conditioned reflexes in both. Serum from schizophrenic patients was also active.

Iordanis and Kuchino[30] studied the effect of adrenochrome on complex behaviour in monkeys. Doses of 0.7 to 1.2 mg. per animal affected learned behaviour for two to five hours. The animals reacted to food and took it out of a basket but did not react to stimuli which signified food. In some cases there were also short sleeplike states. Blood serum from schizophrenic patients had an effect similar to adrenochrome. It always affected learned habits (conditioned reflexes of the monkey up to two hours) and there were catatonic-like symptoms lasting 15 to 20 minutes. When the monkey recovered, the normal reaction to food came back first, then simple habits and finally complex habits.

In his review in *The Lancet*[51] Smythies writes "Thus the results may well have been due to placebo effects, the extraordinary range of which was not fully realized at the time." We are not sure whether he means by this that we were not aware of these placebo effects or that he himself was ignorant of them. Like many others, he may have assumed that anyone who does not pay homage to the double-blind cult must necessarily be ignorant of the effects of anxiety and expectation. We have been running double-blind trials in Saskatchewan since early 1952 and are not naïve in these matters. The issue which we discuss at some length elsewhere[26] is whether or not double-blind studies work. The evidence is doubtful.

The evidence that adrenochrome and adrenolutin produce changes in animals similar to LSD-25 and mescalin is abundant and has been reviewed in some detail by Hoffer.[24] The evidence that they are psychotomimetic in man is not as strong, but all the published accounts of experiments with adrenochrome given to humans have corroborated our original findings.[20, 49, 57] Grof *et al.*[20] presented an abstract of their work to the 3rd International Congress of Psychiatry recently held in Montreal. They used classical double-blind techniques and found that adrenochrome given sublingually produced changes in normal volunteers which were sometimes as strong as those induced in the same subjects by LSD-25. Auditory as well as visual hallucinations were produced. They concluded: "The results of our experiments support the view of the Saskatchewan group that adrenochrome is a potentially psychotogenic substance. The adrenochrome psychosis represents an approximate model of subtle schizophrenic alterations in the area of associative thinking which was stressed by the authors of the Saskatchewan group but neglected by most of the others."

Sourkes gave his talk on May 11, 1961, before this paper appeared, but his recent article appeared more than two months after Grof's communication was available.

Is Adrenochrome Present in the Body?

It is true that there is some controversy about the original Payza and Mahon report.[44] Perhaps there will

be a similar argument about their revised method,[45] but so far this has not appeared. But even if these methods are shown to be wrong, this does not destroy the adrenochrome hypothesis, for numerous authors have inferred that it could be present and many have claimed it is.

A large number of scientists have suggested or have implied that adrenochrome could be a natural metabolite of adrenaline.[2, 6-10, 13, 18, 19, 30, 34, 35, 37, 41, 47, 56]

Other investigators have concluded that adrenochrome is present or have provided evidence that oxidized indole derivatives of adrenaline are present (i.e. adrenochrome and/or adrenolutin) or have shown how adrenochrome can be transferred *in vivo* into adrenolutin or 5:6 dihydroxy-N-methyl indole.[1, 4, 11, 12, 14-16, 25, 29, 31, 32, 38, 40, 42, 43, 46, 48, 50, 52, 54, 55, 58, 59]

In addition it was reported[60] that urine from schizophrenics was rich in aminochromes which resemble adrenochrome and adrenolutin. Four urines sent to them blind by Axelrod were correctly identified by this test. Two specimens were from schizophrenics and two were not. The probability of getting all correct by chance is $(\frac{1}{2})^4$ of 1/16, i.e. at the 0.06 level. They reported that 14 out of 19 urines from schizophrenics were positive compared to 3 out of 20 controls. (Chi sq. for this distribution is about 10, which for one DF is significant beyond 0.001).

Proponents of a new hypothesis are usually biased in its favour. Unfortunately, critics can also be biased against an hypothesis and may show their bias by ignoring evidence. This communication as well as the few references given by Sourkes is as complete as we have been able to make it. If any references are not included, it is because we have not been able to find them. We have only ignored papers where it is claimed on *a priori* reasoning that adrenochrome could not exist in the body. This, after all, is not scientific evidence.

The adrenochrome hypothesis may or may not be corroborated. It may or may not lead to the solution of schizophrenia. Only the efforts of scientists with open minds will settle that question (see Barber[3]).

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REFERENCES

1. ALTSCHULE, M. D.: *J. Neuropsychiat.*, **2**: 71, 1960.
2. BACQ, Z. M.: *Pharmacol. Rev.* **1**: 1, 1949; in *J. Pharmacol. & Exper. Therap.* **95**: April (pt. 2), 1949.
3. BARBER, B.: *Science*, **134**: 596, 1961.
4. BELL, G. H., DAVIDSON, J. N. AND SCARBOROUGH, H.: Textbook of physiology and biochemistry, 4th ed., E. & S. Livingstone, Ltd., London, 1959.
5. BENJAMIN, J. D.: *Psychosom. Med.*, **20**: 427, 1958.
6. BLASCHKO, H. AND SCHLOSSMANN, H.: *J. Physiol.*, **98**: 130, 1940.
7. BRAINES, C. H. *et al.*: Biophysical research in psychiatry. Collected papers, Laboratory of Experimental Pathology, Institute of Psychiatry, Academy of Sciences, Moscow, 1959.
8. BULLOUGH, W. S.: *J. Endocrinol.*, **8**: 265, 1952.
9. *Idem*: *In*: Vitamins and hormones; advances in research and applications, Vol. 13, edited by R. S. Harris, G. F. Marrian and K. U. Thimann, Academic Press, Inc., New York, 1955, p. 261.
10. FELLMAN, J. H.: *J. Neurol. Neurosurg. & Psychiat.*, **21**: 58, 1958.
11. FISCHER, P. AND LANDTSHEER, L.de.: *Experentia*, **6**: 305, 1950.
12. FISCHER, P. AND LECOMTE, J.: *Bull. Soc. chim. biol.*, **33**: 569, 1951.
13. FOLEY, J. M. AND BAXTER, D.: *J. Neuropath. & Exper. Neurol.*, **17**: 586, 1958.
14. GERSHENOVICH, Z. S., KRICHEVSKAYA, A. A. AND ALEKSEENKO, L. P.: *Ukrain. Biokhim. Zh.*, **27**: 3, 1955 (Russian). Abstracted in *Chem. Abstracts*, **49**: 10470 (d), 1955.
15. GOLDENBERG, M. *et al.*: *Arch. Int. Med.*, **86**: 823, 1950.
16. GREEN, S., MAZUR, A. AND SHORR, E.: *J. Biol. Chem.*, **220**: 237, 1956.
17. GREEN, D. E. AND RICHTER, D.: *Biochem. J.*, **31**: 596, 1937.
18. GREIG, M. E. AND GIBBONS, A. J.: *Fed. Proc.*, **16**: 302, 1957 (abstract).
19. GREWAL, R. S.: *Brit. J. Pharmacol.*, **7**: 338, 1952.
20. GROF, S. *et al.*: *In*: Abstracts of papers presented at 3rd International Congress of Psychiatry, Montreal, 1961.
21. HARLEY-MASON, J., LAIRD, A. H. AND SMYTHIES, J. R.: *Confinia neurol.*, **18**: 152, 1958.
22. HOFFER, A.: *In*: Hormones, brain function and behaviour, edited by H. Hoagland, Academic Press, Inc., New York, 1957.
23. *Idem*: *Dis. Nerv. System*, **21**: (2) Supp., 79, 1960.
24. *Idem*: The effect of adrenochrome and adrenolutin on the behaviour of animals and the psychology of man. *In*: International Review of Neurobiology, edited by C. C. Pfeiffer and J. R. Smythies, Academic Press, Inc., New York. In preparation.
25. HOFFER, A. AND KENYON, M.: *Arch. Neurol. & Psychiat.*, **77**: 437, 1957.
26. HOFFER, A. AND OSMOND, H.: *J. Neuropsychiat.*, **2**: 221, 1961.
27. *Idem*: The chemical basis of clinical psychiatry, Charles C Thomas, Springfield, Ill., 1960.
28. HOFFER, A., OSMOND, H. AND SMYTHIES, J. R.: *J. Ment. Sc.*, **100**: 29, 1954.
29. HOFFER, A. AND PAYZA, A. N.: Paper presented at 114th Annual Meeting, American Psychiatric Association, San Francisco, May 12-16, 1958.
30. IORDANIS, K. A. AND KUCHINO, E. B.: *In*: Problems of experimental pathology, edited by C. H. Braines, Institute of Psychiatry, Academy of Sciences, Moscow, 1959.
31. JANTZ, H.: *Zbl. ges. Neurol. Psychiat.*, **137**: 141, 1956.
32. (a) KAUFMANN, H. AND KOCH, E.: *Presse méd.*, **67**: 1141, 1959.
(b) *Idem*: *Rev. Atheroscler.*, **1**: 290, 1959.
33. KETY, S. S.: *Science*, **129**: 1528; 1590, 1959.
34. KISCH, B.: *Exper. Med. & Surg.*, **5**: 166, 1947.
35. KORZOFF, B. A. AND KUCHINO, E. B.: *In*: Problems of experimental pathology, edited by C. H. Braines, Institute of Psychiatry, Academy of Sciences, Moscow, 1959.
36. KUCHINO, E. B.: *In*: Problems of experimental pathology, edited by C. H. Braines, Institute of Psychiatry, Academy of Sciences, Moscow, 1959.
37. LANGEMANN, H. AND KOELLE, G. B.: *Experientia*, **14**: 303, 1958.
38. LECOMTE, J. AND FISCHER, P.: *Arch. internat. physiol.*, **58**: 424, 1951.
39. LORENZ, K.: *Harvey Lect.*, Series 54 (1958-59): 60, 1960.
40. MASLOVA, A. F.: *Biokhimiia*, **24**: 181, 1959.
41. MEIROWSKY, E.: *Brit. J. Dermat.*, **52**: 205, 1940.
42. NOVAL, J. J., BRANDE, B. L. AND SOHLER, A.: *Fed. Proc.*, **18**: 428, 1959 (abstract).
43. OSINSKAYA, V. O.: *Biochemistry*, **22**: 496, 1957.
44. PAYZA, A. N. AND MAHON, M.: *Anal. Chem.*, **31**: 1170, 1959.
45. *Idem*: *Ibid.*, **32**: 17, 1960.
46. PICKWORTH, F. A.: New outlook on mental diseases, Williams & Wilkins Company, Baltimore, Md., 1952.
47. ROSTON, S.: *J. Biol. Chem.*, **235**: 3315, 1960.
48. RIGDON, R. H.: *Surgery*, **8**: 839, 1940.
49. SCHWARZ, B. E. *et al.*: *Arch. Neurol. & Psychiat.*, **75**: 83, 1956.
50. SENOH, S. AND WITKOP, B.: *J. Am. Chem. Soc.*, **81**: 6231, 1959.
51. SMYTHIES, J. R.: *Lancet*, **1**: 1287, 1960.
52. SOHLER, A. *et al.*: *Fed. Proc.*, **20**: 173, 1961 (abstract).
53. SOURKES, T. L.: *Canad. M. A. J.*, **85**: 487, 1961.
54. SULKOWITCH, H. AND ALTSCHULE, M. D.: *Arch. Gen. Psychiat.*, **1**: 108, 1959.
55. SULKOWITCH, H., PERRIN, G. M. AND ALTSCHULE, M. D.: *Proc. Soc. Exper. Biol. & Med.*, **95**: 245, 1957.
56. TAKAHASHI, Y. AND AKABANE, Y.: *Arch. Gen. Psychiat.*, **3**: 674, 1960.
57. TAUBMANN, G. AND JANTZ, H.: *Nervenarzt*, **28**: 485, 1957.
58. UTEVSKII, A. M. AND OSINSKAYA, V. O.: *Ukrain. Biokhim. Zh.*, **27**: 401, 1955. Abstracted in *Internat. Abst. Biol. Sc.*, **6**: 192, 1957, abstract No. 2733.
59. VEECH, R. L. *et al.*: *Arch. Gen. Psychiat.*, **3**: 642, 1960.
60. VEECH, R. L. *et al.*,: *Ibid.*, **5**: 127, 1961.
61. WEINSTEIN, S. AND MANNING, R. J.: *Proc. Soc. Exper. Biol. & Med.*, **32**: 1096, 1935.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

MOULDS IN THE ALIMENTARY CANAL

Most persons are familiar with the appearance of green mould in vomit and in faeces. But it has been looked upon as without importance even in cholera nostra and infantile diarrhoea, where it is the most prominent symptom. I judge it to have a causal relation to these conditions for the following reasons:

(1) Mould is present often when no other sufficient cause of the symptoms can be found.

(2) It is present in abundance in some of our most fatal diseases.

(3) Its partial destruction is followed by immediate improvement.

(4) Its complete removal in such cases is an essential element in recovery.

—I. Proctor Hall, *Canad. M. A. J.*, 1: 1162, 1911.

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MEDICAL NEWS IN BRIEF

AORTIC PRESSURES DURING CLOSED-CHEST CARDIAC MASSAGE

Gurewich *et al.* report an episode of ventricular fibrillation during retrograde left-heart catheterization that afforded an opportunity to obtain direct aortic pressure measurements while closed-chest cardiac compression was being performed (*Circulation*, 23: 593, 1961).

Direct arterial pressure recordings in this case illustrated that rhythmic, manual compression of the lower sternum can produce a substantial blood pressure in the distal aorta during ventricular fibrillation. Coincident improvement in the patient's colour suggested that this was associated with a significant peripheral flow of oxygenated blood. A pressure of 80/40 mm. Hg was immediately obtained and maintained thereafter without difficulty throughout the period of closed-chest massage. This level compared favourably with the patient's earlier, resting arterial pressure of 70/40 mm. Hg, but was slightly less than the pressures obtained by open-chest, manual cardiac massage, which averaged around 100/70 mm. Hg.

The attractive features of closed cardiac compression include its simplicity, ease of application, and general applicability regardless of place and regardless of whether the heart is in standstill or fibrillation. Valuable time may be gained through this method for obtaining other resuscitative equipment, such as an electric external pacemaker and defibrillator.

This appears to be the procedure of choice in the treatment of cardiac arrest occurring outside the operating room or where an external pacemaker or defibrillator is not immediately available.

GANGLION-BLOCKING AGENTS IN INSULIN SHOCK THERAPY

Insulin shock therapy is one of the most effective forms of treatment in early schizophrenia. Its use has been discontinued in many hospitals for technical reasons, particularly because of the time interval before the first coma is produced. This time interval is dependent to a great extent on the response of the insulin antagonists. The faster the increase of the insulin dose, the greater the stimulation of the antagonistic mechanism. The latter can only function, however, when the sympathetic nervous system is intact. On the basis of these considerations the use of ganglion blocking agents in conjunction with insulin has been tried by St. Hift (*Wien. klin. Wchnschr.*, 73: 430, 1961).

Hexamethonium was found to be a suitable preparation. Preliminary tests were carried out to determine the optimal dose which would produce a satisfactory blocking effect without lowering the blood pressure appreciably. The following schedule was worked out: On the first day 400 mg. of hexamethonium is given orally, followed by 20 units of insulin one hour later. After another hour, 40 mg. of hexamethonium is administered subcutaneously. The amount of insulin is increased daily by 20 units, whereas the dose of hexamethonium remains constant. The first coma usually occurs after four to six days, i.e. with an insulin dose of 80 to 120 units. After four comas the parenteral hexamethonium is replaced by tablets and is then gradually discontinued.

In rare cases, coma was not produced with 140 units of insulin, and the hexamethonium had to be increased to a maximum of 800 mg. orally and 60 mg. subcutaneously.

The course of the coma is not altered by hexamethonium. Most patients are quieter in the precomatose phase, and sedatives are rarely necessary. During the four years of its use St. Hift did not encounter any serious side effects caused by hexamethonium. He feels that there is less danger of a protracted coma because high doses of insulin are avoided. In the 145 patients treated with hexamethonium the average initial coma dose was 92 units of insulin, and the average time interval before the first coma was 5.3 days. The corresponding figures before the use of hexamethonium were 296 units of insulin and 14.7 days.

MULTIPLE CONGENITAL ABNORMALITIES ASSOCIATED WITH CHROMOSOMAL TRISOMY

An infant girl with multiple congenital abnormalities consisting of a cerebral defect, micro-ophthalmia, low-set ears, short neck, polydactyly, hemangiomas, umbilical hernia, and spinal abnormalities, associated with trisomy of an acrocentric chromosome (Denver Group 13-15) in the cells of the blood and skin, is described by Atkins and Rosenthal (*New England J. Med.*, 265: 314, 1961).

The patient's mother and father were healthy; her 5-year-old brother was normal; and her 3½-year-old brother had phenylketonuria and was mentally retarded. There was no other family history of congenital abnormalities. Cytologic studies were carried out on cultured leukocytes from the patient's mother and both brothers; their chromosomes appeared normal.

The probable cause of trisomy in this case was meiotic nondisjunction during parental gametogenesis. The finding of the same chromosome pattern in both the blood and the skin of the patient is against the possibility that a mosaic arose as a result of mitotic nondisjunction after fertilization. The similarity of this case to cases previously reported is strong evidence in favour of the congenital defects in this patient being directly related to the extra autosome. The presence of multiple congenital defects (with the exception of one normal man) in the other reported cases of autosomal trisomy is further evidence of a causal relation between the chromosomal abnormality and the phenotype in the present case.

In contrast to mongolism and the sex-chromosome disorders, the examples of congenital defects with chromosomal abnormalities so far described are not sufficiently similar to permit definite conclusions about the effects of specific chromosomes upon the human phenotype.

(Continued on advertising page 28)

ASSOCIATION NEWS

THE FIFTY-SIXTH ANNUAL MEETING OF THE ALBERTA DIVISION, THE CANADIAN MEDICAL ASSOCIATION

The 56th Annual Meeting of the Alberta Division, The Canadian Medical Association, was held in the Macdonald Hotel, Edmonton, from September 25 to 28, 1961, under the presidency of Dr. E. F. Donald of Edmonton.

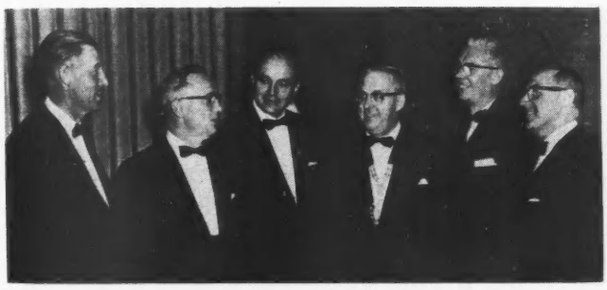
The large attendance at the scientific sessions spoke eloquently of the quality of the program which had been arranged. Guest speakers from outside the province included Dr. Joel W. Baker, Surgeon in Chief, Virginia Mason Hospital, Seattle, Washington, who spoke on "Pitfalls in Surgery of the Biliary Tract", and also addressed the Alberta Surgical Society on the subject "The Surgical Decompression of Intestinal Obstruction with Reference to a Specific Method". Dr. James Darragh, Montreal General Hospital and McGill University, dealt with "The Management of Non-Toxic Goitre" and "The Use of Oral Hypoglycemic Agents in Diabetes Mellitus". Dr. A. S. Ross, Physician-in-Chief, Montreal Children's Hospital, spoke on "The Rare Disease". Dr. John L. McKelvey, Professor and Head of the Department of Obstetrics and Gynecology of the University of Minnesota, discussed problems of so-called carcinoma *in situ* of the cervix.

At the annual banquet and dance, Dr. A. A. Dixon was installed as President of the Alberta Division. Dr. G. W. Halpenny, President of the C.M.A., removed the Badge of Office from Dr. E. F. Donald and installed Dr. Dixon as President for the forthcoming term of office. During the business session, Dr. R. K. Thomson of Edmonton was elected to the position of President-Elect of the Alberta Division. Dr. Halpenny also installed, *in absentia*, as Senior Members of The Canadian Medical Association Dr. Melvin Graham of Ponoka and Dr. D. M. MacCharles of Medicine Hat; unfortunately, both doctors to be honoured were in hospital at the time of the meeting. The Annual Meeting also elected to Life Membership in the Alberta Division Dr. William Franklin Carscallen of Calgary, Dr. Mildred Folinsbee Newell of Edmonton, Dr. George Franklin Young of Calgary and Dr. Morley Alphonso Ryerson Young of Lamont.

The business sessions and committee reports indicated that the Divisional committees had been working hard during the year. The following are a few of the more interesting highlights from their reports.

The Special Committee on Prepaid Medical Care has carried out a survey amongst the general population of the province to determine, among other things, the percentage of population covered by some form of prepaid medical care and to try to determine any areas of unmet needs throughout the province. The questionnaire also included attitudinal questions on the opinion of individuals as to various forms of prepaid medical care. It is expected that the survey will provide much information which will be of benefit to the committee preparing a brief to be presented to the Royal Commission on Health Services when it sits in this province.

In addition to reporting on short courses held throughout the year, the Committee on Education



Above, left to right, are: Dr. E. F. Donald, Edmonton, Past President of the Alberta Division; Dr. W. Bramley-Moore, Edmonton, Secretary-Treasurer, Alberta Division; Dr. A. A. Dixon, Calgary, newly elected President of the Alberta Division; Dr. G. W. Halpenny, Montreal, President of the C.M.A.; Dr. J. W. Kettlewell, Edmonton, Assistant Secretary, Alberta Division; and Dr. A. F. W. Peart, Toronto, Deputy General Secretary, C.M.A.

indicated that the University of Alberta is considering the appointment of a full-time co-ordinator of continuing education who will have university rank and affiliation. He would be concerned not only with continuing education for the general practitioner but would co-ordinate graduate training programs throughout the province.

The Committee on Maternal Welfare recorded the lowest maternal mortality rate in the province, only 0.17 per 1000 births. It is felt that the work done by this committee in the past has helped materially in bringing about this favourable mortality rate.

The Committee on Medical Aspects of Traffic Accidents has during the past year co-operated with the Provincial Department of Highways in setting up standards for examination of drivers applying for drivers' licences in the province. Every effort has been made to remove the onus of making decisions regarding the eligibility of certain problem applicants for drivers' licences from the individual practitioner where strong personal bias may exist and/or where public relations with the medical profession may be affected by adverse decisions. Problem cases are referred to a panel of specialists who decide whether or not a driver's licence should be granted.

Dr. Joel W. Baker (left), guest speaker from Seattle, Wash., admires the Badge of Office of the C.M.A. President, Dr. G. W. Halpenny, of Montreal. Dr. E. F. Donald of Edmonton, Past President of the Alberta Division, looks on with interest.

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The Committee on Hospital Relations and Professional Services reported on studies to consider the feasibility of a province-wide tissue audit. Regulations under the new Hospitals Act require that all tissues removed at operation be forwarded to a pathologist and accompanied by a form giving all the information for a comprehensive tissue audit. It is proposed that a copy of this information be forwarded to the office of the College of Physicians and Surgeons and the information transferred to I.B.M. cards for use in preparing the necessary statistical information. The Committee feels strongly that this would be an important step towards insuring a continuing high standard of medical care for the people of Alberta, and that it should be carried out by the doctors themselves. They feel that this tissue audit would be a good start in the right direction.

The Executive Committee of the Division has considered the possibility of the Provincial Government's entering into the provision of outpatient radiological and laboratory services under the Alberta Hospitals Act. It is hoped that private radiological offices and pathological laboratories might be considered as approved facilities under the Act. Information about the cost incurred in radiological and laboratory offices was obtained in co-operation with the Alberta Society of Pathologists and the Alberta Society of Radiologists. It was recommended that if the services were made available under the Hospitalization Benefits Act, arrangements should be made whereby payment would be on a fee-for-service basis through Medical Services (Alberta) Incorporated.

The Perinatal Mortality Committee, which for the past six years has studied all registered stillbirths and all deaths of live-born infants of 1000 grams and over who died on or before the seventh day of life, reported a very commendable drop in the perinatal death rate, from 24.2 in 1955 to 20.0 in 1960.

J. W. KETTLEWELL

THE MEDICO-LAY AFFILIATES OF THE CANADIAN MEDICAL ASSOCIATION

CANADIAN SOCIETY OF LABORATORY TECHNICIANS

[This is the tenth of a series of articles describing the organization and work of the voluntary health agencies and other medico-lay bodies affiliated with The Canadian Medical Association.]

BYRON F. WOOD, B.A.,
Executive Secretary

BY AUTHORITY of the Companies Act, the Canadian Society of Laboratory Technologists was incorporated under Dominion Charter in May 1937 for the following purposes and objectives: to improve the qualifications and standing of laboratory technicians in Canada; to promote research endeavour in all branches of laboratory work; to promote a recognized and professional status for technicians; to promote closer co-operation between the medical profession and the technician; to aid more efficiently in diagnosing and treating disease. The operations of the Society are carried on throughout the Dominion of Canada and elsewhere.

The Society represents all the members. Thus a member is first a member of the Society, and second a member of a Branch and/or an Academy. The administration of the national organization is carried on for the members by an Executive Committee. Policy, professional standards, membership, registry, scientific publications and all other matters which are the common concern of the membership as a whole are dealt with by the membership through the Executive Committee and its agencies (Science Sections, Boards and Committees).

The Branches assume responsibility for dealing with matters of particular concern to C.S.L.T. members within their geographical area. One of their major functions is to promote the advancement of medical technology with the area by sponsoring the types of activity that can best be organized and used within such an area.

The Academy is the basic unit of organized membership. Its main concern is increased scientific, technical and social interest for members of the district. It must meet at least four times a year in order to maintain academy status. It is responsible for maintaining liaison with the Branch and must submit an annual report of its activities. Medical representation on a national level is achieved through the Advisory Council.

Acting under the authority of its Charter, the Canadian Society of Laboratory Technologists has established the "R.T." (Registered Technician) as the standard of qualification for the practice of medical laboratory technology which is recognized across Canada. It maintains a Register of medical laboratory technologists in the Dominion. It issues certificates of qualification based on examinations which it conducts uniformly across Canada. These examinations are based upon a syllabus prepared by the Society and revised from time to time. Until June 1960, the certificates were of two classes, general and specialty, the special fields being histology, serology, biochemistry, bacteriology, hematology, parasitology, and blood bank technique. In 1960 the Society, through its newly established Certification Board, made provision for and is now granting additional levels of certification, namely Advanced R.T., Licentiate, and Fellow. At the present time, approximately 4000 holders of the "R.T." are actively engaged in the practice of medical technology across Canada.

The official publication of the Society is the *Canadian Journal of Medical Technology*, published six times a year. The Editor is Anne M. Graham, B.A., R.T., Hamilton, Ont.

The executive offices of the Society are at 99 Wentworth Street South, Hamilton, Ont.

BOOK REVIEWS

RADIOACTIVITY IN MAN. Whole Body Counting and Effects of Internal Gamma Ray-Emitting Radioisotopes. A Symposium held at the Vanderbilt University School of Medicine. Edited by George R. Meneely. 491 pp. Illust. Charles C Thomas, Springfield, Ill., 1961. $16.50.

The title of this book might at once lead to some confusion, suggesting to the general physician that it contains tests using radioactive isotopes in clinical cases. However, this is not the case. The content of the book is taken from a symposium held at Vanderbilt University School of Medicine and edited by George R. Meneely, M.D., and the material was supplied by 48 expert contributors. This has to do, not with the use of radioactivity as tests for disease in man, but rather with the problems of radiation in human beings and radiologic, medical, sociological and legal problems arising from small and increasing burdens of such radioactivity in humans. The effects of fallout are detailed and various counting methods are discussed for determining what radioactivity, and of what type, is present in a human being under consideration.

This, then, is not a book for a practitioner in medicine, nor is it a handbook for a practitioner in nuclear medicine. It is really a high-grade study of the effects of radioactivity from various sources as we note them in the human being—that is, external sources, internal sources, etc.—and as such is a book with limited usage in the field of medicine except for those individuals concerned with this particular problem, viz. the health radiation problem. It is a well-written book, well presented, and certainly the material is extremely carefully documented and authoritative. It would be of interest to health radiation physicists throughout the world, especially those who are concerned with the sociological and legal problems arising therefrom.

RADIATION PROTECTION AND DENTISTRY. The Postgraduate Dental Lecture Series. Arthur W. Wuehrmann. 238 pp. Illust. The C. V. Mosby Company, St. Louis, Mo., 1960. $6.50.

Dr. Wuehrmann has presented a well-written, clearly illustrated, concise handbook on dental radiation, its uses, hazards, and methods of protection.

While this treatise is written primarily for the general practitioner in dentistry, it is also of great value to those utilizing radiation for the purpose of interpretation leading to diagnosis in the various branches or specialties of the medical and dental fields.

The author presents the text in a simplified, informative and readily readable form. This handbook points out the value of radiation and the advantages accruing to the medical and dental professions from its use, and also the responsibility that rests with the dentist and the medical practitioner to protect not only himself but the patient whom he serves.

A synopsis (survey of the literature) is presented in which various articles published in the lay press are listed and commented upon.

A terminology glossary is presented, as well as an appendix on an addendum to the National Bureau of Standards handbook on the "Maximum Permissible Exposure to Man".

Specific sections of the text are devoted to the speed and types of films, limitation of the x-ray beam, and suggested equipment for protective measures to be used in special cases such as excessive radiation and pregnancy.

With the increase in knowledge concerning the many problems of radiation, this handbook, which is part of a postgraduate dental lecture series, becomes of increasing importance and value to the dentist and medical practitioner alike.

"Radiation Protection and Dentistry" will prove a valuable addition to dental and medical libraries.

BILE PIGMENTS IN HEALTH AND DISEASE. American Lecture Series. C. H. Gray. 95 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1961. $5.50.

The author indicates that the present volume is intended "to supplement and not supplant" his earlier book published in 1953. This goal is accomplished admirably, since the first volume emphasized the chemical details, whereas the present one is written from the clinical aspect. The chapters are well organized and written, and the book stands as an excellent account of the present biochemical knowledge of the bile pigments. A most welcome feature is the frequent inclusion of summary tables which are so indispensable for study or reference. The information is gathered from experts in this field from England, United States, Australia, Japan and Czechoslovakia, as well as from the author's own publications, and is supported by some 285 references which are arranged alphabetically at the end of each chapter.

Chapter I gives a brief introduction to the essential chemical structure in relation to some of the reactions of the bile pigments. The latest work in hemoglobin breakdown and bile pigment formation is discussed in chapter II, while the urobilinoid pigments are reviewed in chapter III. The van den Bergh reaction is discussed in chapter IV. It is shown that bilirubin is conjugated with glucuronic acid to give a water-soluble direct reacting compound, and that the function of alcohol in the indirect reaction is not to split a bilirubin-protein bond, but to enable the bilirubin to pass into true solution for the reaction to take place. Also, the precise nature of the positive direct reaction is related only to the concentration of bilirubin and not to any special clinical condition. The presence of bile pigments in the body fluids and tissues in chapter V is followed by some investigational work (mainly isotopic) on hemoglobin metabolism in chapter VI. Biosynthesis of bilirubin glucuronide is shown in chapter VII to be brought about by liver microsomal preparations. However, it is indicated that further work needs to be done along these lines since such conjugation may also occur to some extent in extrahepatic tissues. The last two chapters are devoted to the classification and description of the various clinical forms of jaundice as well as the technique and clinical interpretations of the tests.

In the reviewer's opinion, the author has succeeded in producing a concise, authoritative and up-to-date book which should be valuable as a reference source not only for the clinician and medical student but also in a routine biochemical laboratory as well as to the research worker in this field.

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LES GRANDES ACTIVITES DU RHINENCEPHALE. VOL. 1. ANATOMIE DU RHINENCEPHALE. Semaine Neuro-Physiologique de la Salpêtrière. H. Gastaut and H. J. Lammers. 166 pp. Illust. Masson & Cie, Paris, 1961. 22 NF. (approx. $4.65).

LES GRANDES ACTIVITIES DU RHINENCEPHALE. VOL. II. PHYSIOLOGIE ET PATHOLOGIE DU RHINENCEPHALE. Semaine Neuro-Physiologique de la Salpêtrière. Various authors. 337 pp. Illust. Masson & Cie, Paris, 1961. 43 NF. (approx. $9.05).

One feature of brain research in the postwar years has been the intense concentration on the functions and connections of particular anatomical areas of the nervous system. The frontal, parietal, and temporal lobes have each been a topic for symposia and published volumes, while the reticular activating system has also been much discussed of late. No area of the brain has aroused more interest among neurophysiologists, psychologists and psychiatrists, recently, than the rhinencephalon—one of the oldest and most important regions of the mammalian brain. As the name indicates, its association with the olfactory sense has long been known, but appreciation of its relationships to memory and to emotion has arisen from recent and exciting discoveries of great significance for human knowledge.

The papers included in these two volumes were presented at a symposium held in Paris some four years ago. Volume I by Professors Gastaut and Lammers gives a detailed and valuable account of the complex anatomy and connections of the rhinencephalon. Volume II contains 12 papers on its physiological and clinical aspects, by a number of European and North American workers, including Dr. Peter Gloor of the Montreal Neurological Institute.

Much new experimental work on the rhinencephalon has appeared in the intervening four years. Nevertheless, these two volumes will remain a useful contribution to this expanding field of knowledge. They will be of particular interest to neurophysiologists and to neurologists and psychiatrists who are trying to bridge the narrowing gap between "brain" and "mind".

ESSENTIALS OF ELECTROCARDIOGRAPHY. N. S. Variava. 72 pp. Illust. Current Technical Literature Co. Private Ltd., Bombay, 1961. Rs. 10. (approx. $2.20).

The author states in the Preface of this pocket-sized volume that his intention in recording the basic or essential facts of electrocardiography in as plain language as possible is to enable the practising physician who has had no special training in the subject to interpret the records that he takes on his own patients.

This little book is published on rather inferior paper, but it does have illustrations that can be understood by those without any special knowledge of electrophysiology or anatomy. The illustrations of electrocardiographic patterns in the later chapters of the book are typical examples, but as it takes considerable time to become acquainted with the range of these various patterns, one wonders if it really would be of sufficient help to prove of value to a man in practice who had had no training in this area of medicine.

The second aim of the book as stated by the author is to prove of value to undergraduate and postgraduate medical students studying for their professional examinations. To this reviewer it appears that this volume is better suited to this latter task of launching a student on his study of electrocardiography, realizing that these are simply the bare essentials.

There is one shortcoming which seems important in this day and age, i.e. the author has made no reference to the fact that the electrocardiogram is simply a reflection from one aspect of the vectorelectrocardiogram. Without the latter concept, much of what he portrays and asks the student to learn becomes empirical detailed data which may not be properly understood.

In summary, one doubts that the author has succeeded in accomplishing his first objective of providing sufficient information to allow a general practitioner with no knowledge of electrocardiography to start taking and interpreting his own records. There is probably enough information to enable an undergraduate student or a recent graduate student to gain the bare essentials of electrocardiography.

ORTHOPAEDIC APPROACHES. A Stereographic Manual. Section I. Lower Extremity. Reels 1 to 18. John J. Joyce III and Michael Harty. 80 pp. Illust. The Williams and Wilkins Company, Baltimore, Maryland, 1961. $28.00.

This book represents a visual, three-dimensional approach to the surgical anatomy of the lower extremity.

It is highly recommended for both the resident orthopedic surgeon as a concise text of operative approaches to the lower extremity and, as well, for the practising orthopedic surgeon as an integrated review of the lower extremity. It is to be hoped that this endeavour may reach the medical student as well.

There are 18 View-Master reels making up 126 well-labelled, full-colour views. These photographs are high-quality reproductions of the successive surgical steps of the various operative procedures in the lower extremity.

The several important approaches to operative areas in the lower extremity are included. Thus, whether the surgical problem indicates an anterior, lateral, medial or posterior approach, or whether the orthopedic surgeon has an individual preference with respect to technique, the surgical anatomical answer is to be found in this text.

Each operative area is discussed in terms of general remarks, indications, limitations, positioning of the patient, guide posts, danger points, and a description of the procedure. These logical, integrated descriptions nicely complement the three-dimensional views. Further, the text is written so as to correlate accurately with these pictures.

The text itself is well illustrated, and also contains a large number of black-and-white photographs. A folding View-Master is included on the inside cover of the text.

THE EAR, NOSE AND THROAT DISEASES OF CHILDHOOD. J. F. Birrell. 382 pp. Illust. Cassell & Co. Ltd., London; British Book Service (Canada) Ltd., Toronto, 1960. $9.00.

There are few textbooks devoted entirely to the problems of ear, nose and throat diseases of childhood. This book is a worthwhile contribution on the subject, and will be of interest to all medical personnel who are intimately concerned with the management of the physical ills of the young.

The subject matter is generally well covered in a practical and precise manner. It is very easy and most interesting to read.

Canad. M. A. J.
Dec. 9, 1961, vol. 85

ANNOUNCING
Canadian Life Insurance
MEDICAL FELLOWSHIPS

The life insurance companies in Canada have, since 1949, been making available a limited number of fellowships for the purpose of strengthening and developing further programs of medical research in the universities of Canada. These fellowships are awarded through the Standing Committee on Public Health of The Canadian Life Insurance Officers Association on the recommendation of a Medical Advisory Committee.

The project as presently set up provides that fellowships aggregating $60,000 will be awarded each year and that not more than one fellowship will be awarded to each of the twelve medical schools in Canada. However, if some medical schools are not in a position to submit applications, or submit applications which do not meet with the approval of the Medical Advisory Committee, it will be possible to consider a second, or even a third, application from a single medical school.

Qualifications:

Applicants must have a doctor's degree in medicine or in one of the basic medical sciences or the equivalent. They should have a pronounced interest in, and aptitude for, research or teaching, and should be regarded by the administration of the school as possible candidates for a teaching or research appointment in a medical school. Moreover, during the tenure of their fellowship, they should be appointed in some capacity to the teaching or research staff of the medical school in which they are working.

Awards:

The amount of a Canadian Life Insurance Medical Fellowship is $5,000.

Term:

Fellowships are awarded on an annual basis, but may be renewed for a further period of two years, depending on the progress reports of the work in hand. Fellowships will run from July 1st to June 30th each year (with exceptions in special cases).

Reports:

Progress reports of the work undertaken are required. These reports, however, need not exceed two pages in length and should be confined to the work aided by the fellowships. Extensive tables, charts, photographs and typescripts of articles are not necessary.

Applications:

Application forms and further information about regulations concerning Canadian Life Insurance Medical Fellowships may be obtained from the deans of medical schools. Applications must be submitted by the dean and recommended by him. They must be filed not later than February 14th of each year and forwarded to:

The Secretary
Standing Committee on Public Health
The Canadian Life Insurance Officers Association
302 Bay Street
Toronto, Ont.

THE CANADIAN LIFE INSURANCE OFFICERS ASSOCIATION

NEWS & VIEWS
ON THE ECONOMICS OF MEDICINE

Prepared by the Department of Medical Economics. The Canadian Medical Association

DEC. 9, 1961, NUMBER 21

Our sources of information are private communications and published comments in medical journals and the lay press. These are usually reliable but incorrect quotation or interpretation is always possible.

The Present Situation in Saskatchewan

The present attitude of the doctors of Saskatchewan toward the recently enacted legislation may be stated succinctly: Dr. H. D. Dalgleish, President of the College recently stated that the profession will not negotiate on the basis of the present bill.

This state of affairs has arisen because neither the majority report of the Thompson Advisory Committee on Medical Care, nor the Government decisions reflected in the Act, took into account the proposals advanced by the profession. In fact, the differences between the new legislation and the outline which Mr. Douglas announced in December 1959 are so minor that one could label the time and expense of the Thompson Committee as a wasted effort.

The report of the Thompson Committee was presented in three sections: the Majority Report which forms the basis of the new Act; a Minority Report, signed by the three representatives of the College and the representative of the Chamber of Commerce, which reiterated the profession's opposition to a compulsory program controlled by government and recommended the profession's proposal of assistance in depth to those persons in need; and a third report, of dissenting views, signed by the representative of the Saskatchewan Federation of Labour, which agreed with the Majority Report but demurred because it did not go as far as Labour had suggested.

Immediately upon presentation of the Committee report, Mr. Douglas and his government announced the terms of "An Act to provide for Payment for Services rendered to Certain Persons by Physicians and Certain other Persons". This provides for compulsory participation by all members of the public in the financing of the Saskatchewan Medical Care Insurance Act administered by a Commission, responsible to the Minister of Health through his Deputy. This Commission is given almost unlimited power, subject only to the dictates of the Government, to determine which doctors will be eligible to receive payment for services and what the method and amount of payment shall be.

The medical profession, not unnaturally, refuses to accept this proposal. Adding to this basic opposition is their knowledge of the actions and the reversal of actions which the Government has previously taken during its 17 year tenure of office. The Government's past record in dealing with the profession is not such as to engender confidence in future negotiations.

Thus, the impasse. Government must implement this legislation which it has inherited from Mr. Douglas and the profession refuses to work on the basis outlined. The support of the individual members of the profession is shown by the near-unanimous vote on the following resolution at the recent annual convention of Saskatchewan doctors:

WHEREAS THE COLLEGE OF PHYSICIANS AND SURGEONS OF SASKATCHEWAN ENDORSES THE PRINCIPLE OF UNIVERSAL AVAILABILITY OF PREPAID MEDICAL INSURANCE AND HAS SO STATED ON NUMEROUS OCCASIONS, AND

WHEREAS WE BELIEVE THAT THE BEST INTERESTS OF OUR PATIENTS HAVE BEEN REFLECTED IN THE PERSONAL SERVICES THEY HAVE ALWAYS RECEIVED FROM US, AND

WHEREAS THE MAINTENANCE AND IMPROVEMENT OF THE PRESENT HIGH STANDARDS OF MEDICAL CARE WILL BE ADVERSELY AFFECTED BY THE PRESENT BILL,

THEREFORE THE COLLEGE OF PHYSICIANS AND SURGEONS OF SASKATCHEWAN, THE SASKATCHEWAN DIVISION OF THE CANADIAN MEDICAL ASSOCIATION, REITERATES ITS REFUSAL TO ACCEPT A GOVERNMENT CONTROLLED MEDICAL SCHEME AS OUTLINED IN THE LEGISLATIVE DRAFT SENT TO THE MEMBERS BY THE MINISTER OF PUBLIC HEALTH, AND DECLARES THAT IT CANNOT CO-OPERATE IN SUCH A PLAN.

****

Saskatchewan Newsletter, November 28, 1961.

"Medical Care Bill

The Medical Care Bill received its 3rd and final reading in the Legislature on Friday, November 17th. We understand no substantial changes were made in its provisions. The vote was reported to be on party lines - 30 for and 16 against. The Bill received much criticism in the House.

New Minister of Health

A change in the Cabinet portfolio of Public Health was announced by Premier Lloyd Tuesday, November 21st, 1961.

Minister Walter Erb, appointed in 1956, leaves the Department of Health and the Hon. W. G. Davis, 46, former Executive Secretary of the Saskatchewan Federation of Labour from Moose Jaw, assumes the Cabinet post of Minister of Public Health. Mr. Davis had been appointed Public Works Minister last year.

Mr. Walter Smishek of Regina, a member of the Advisory Planning Committee on Medical Care, who contributed his dissenting views in Chapter VII of the Interim Report of the Advisory Planning Committee, is the present Executive Secretary of the Saskatchewan Federation of Labour".

CLASSIFIED ADVERTISEMENTS

Please send copy to the Advertising Department, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

Rates: $7.00 for each insertion of 40 words or less, additional words 10c each.

If a box number is required, there will be an additional charge of 50c on the first advertisement to cover postage and handling charges.

The publishers of the Canadian Medical Association Journal are constantly on the alert for misrepresentations in classified advertisements. However, it is not always possible to detect inaccuracies. The publishers therefore urge all respondents to investigate thoroughly the opportunities offered in these pages before any commitments are made.

Classified advertisements must be at the office of the Journal not later than three weeks prior to date of issue.

Fellowships

PEDIATRIC TEACHING AND RESEARCH FELLOWSHIP available July 1, 1962. Remuneration $8000 per annum. Excellent facilities available for a continuing respiratory disease study with vaccine trials. Approved for fellowship training by the Royal College of Physicians and Surgeons of Canada. Applicants must have at least two years' experience in pediatrics. Apply to Medical Director, Regina General Hospital, Regina, Saskatchewan.

Positions Wanted

ANESTHETIST seeks opening. Certification requirements completed. Reply to Box 109, CMA Journal, 150 St. George St., Toronto 5, Ont

CANADIAN SURGEON AGE 34, F.R.C.S.[C], F.A.C.S., C.S.P.Q., wishes to relocate from large city. Clinic or group anywhere in Canada considered. Reply to Box 97, CMA Journal, 150 St. George St., Toronto 5, Ont.

KEEN YOUNG PRACTITIONER, married, Protestant, with 4 years' G.P. experience; 3 in Canada, seeks opening in Alberta, commencing January. Reply to Dr. H. M. O. Brown, c/o Selkirk Hotel, Jasper Ave., Edmonton.

LONG TERM LOCUM TENENS OR ASSISTANTSHIP desired beginning January 1, 1962. Preference for Ontario but other provinces considered. Previous experience in general practice. Apply to Box 110, CMA Journal, 150 St. George St., Toronto 5, Ontario.

MIDDLE-AGED DOCTOR with considerable business experience requires position as a medical administrator, preferably in the Toronto area. Reply to Box 111, CMA Journal, 150 St. George St., Toronto 5, Ont.

WOMAN GRADUATE, L.M.C.C. seeks opening in general practice. Willing to locate anywhere in Canada. Reply to Box 116, CMA Journal, 150 St. George St., Toronto 5, Ontario.

Positions Vacant

AN OPPORTUNITY EXISTS FOR GENERAL PRACTITIONER in rural town. Well-equipped 18-bed hospital with one other doctor on medical staff. For full particulars contact: G. L. McMorran, Chairman of Board, Reston Community Hospital, Reston, Man.

APPLICATIONS ARE INVITED FOR THE FULL-TIME POST OF RADIOTHERAPIST due to expansion of services. Salary scale—$10,000-$14,000 per year. Starting salary according to experience. Pension plan and other benefits. Apply with full particulars and two testimonials, to the director, British Columbia Cancer Institute, 2656 Heather Street, Vancouver 9, B.C.

ASSISTANT REQUIRED FOR BUSY GENERAL PRACTICE in Niagara Peninsula. Good office and hospital facilities. Good salary and car allowance. Interview to be arranged. Reply, giving full particulars and date available to Box 112, CMA Journal, 150 St. George St., Toronto 5, Ont.

ASSISTANT REQUIRED in general practice by January 1, 1962, in prosperous southern Ontario town of 2600, in association with a well-established general practitioner. This office has had associates for fifteen years. Excellent vicinity for schooling and recreation, e.g., golfing, skating, bowling, curling, etc. References must accompany applications. Please state age, religion, salary expected and marital status to Box 46, CMA Journal, 150 St. George St., Toronto 5, Ont.

ASSISTANT WANTED for busy practitioner in Niagara Peninsula. Medicine, surgery, obstetrics and industrial work. Apply to Box 82, CMA Journal, 150 St. George St., Toronto 5, Ontario.

ASSISTANT wanted for interesting general practice, 120 miles from Toronto, general hospital in town; living quarters available. Definite view to permanent association if mutually satisfactory. Salary $700 per month. Must have own car. Position becomes vacant by July 1, 1962. Apply to Box 71, CMA Journal, 150 St. George St., Toronto 5, Ont.

CHIEF MEDICAL INVESTIGATOR to direct new state-wide medical investigation system. Must be board certified pathologist with preferably some training in forensic medicine and eligible for licensure to practice medicine in Oregon. Starting salary open depending on qualifications within range of $15,960 to $17,700. Civil Service, Social Security, and State Retirement Coverage. Write: A. T. Johnson, Pers. Dir., Oregon State Board of Health, P.O. Box 231, Portland 7, Oregon.

EXCEPTIONAL OPPORTUNITY FOR WELL QUALIFIED YOUNG G.P. to join group practice in one of the most rapidly growing communities in southern California. Modern fully-equipped clinic, 45 minutes from central Los Angeles. Guaranteed salary plus percentage and opportunity for full partnership within one year. Living quarters in new home provided. Must be eligible for California licence. Write stating qualifications to J. Manny Shore, M.D., 6221 Wilshire Blvd., Los Angeles 48, California.

FULL AMERICAN BOARD approved training program is available at University Teaching Hospital. Applicants must have ECFMG certificate. Apply to Director of Pathology, Western Reserve University at Cleveland Metropolitan General Hospital, 3395 Scranton Road, Cleveland 9, Ohio, U.S.A.

GENERAL PRACTITIONER for active, well-established clinic, composed of seven general practitioners. A certified obstetrician and gynecologist would be considered. Over 400 confinements in 1960. Opportunity for partnership after one year. Apply to Business Manager, Lloydminster Clinic, Lloydminster, Sask.

GENERAL PRACTITIONER WANTED for group in interior British Columbia. Active group and many opportunities to advance professional interests. Modern, well-equipped accredited hospital. Partnership program. Attractive salary and numerous fringe benefits. Reply to Box 99, CMA Journal, 150 St. George St., Toronto 5, Ont.

MANITOBA REHABILITATION HOSPITAL, WINNIPEG, MANITOBA: Specialist in physical medicine and rehabilitation. —Applications are invited from physicians qualified in this field. The appointment is full-tme. Salary (minimum $10,000) depending on qualifications and experience. The hospital is at present under construction. It will be opened early in 1962, will contain 158 beds and has been specifically designed as a rehabilitation centre with all modern facilities for the treatment of in-patients and out-patients. The hospital is within the medical centre, close to general hospitals and medical college. It will contain the school of physiotherapy and occupational therapy of the University of Manitoba. A wide variety of patients will be accepted and facilities provided for research in physical medicine and rheumatology. The successful applicant may be required to give additional consultant services in physical medicine elsewhere in the Province of Manitoba. Apply to the Chief of Medical Services, Dr. L. H. Truelove, Sanatorium Board of Manitoba, 1654 Portage Avenue, Winnipeg, Manitoba.

(Continued on page 24)

CLASSIFIED ADVERTISEMENTS

NEUROSURGERY.—Assistant wanted. Large Canadian city. Good salary. Apply to Box 113, CMA Journal, 150 St. George St., Toronto 5, Ont.

OPHTHALMOLOGIST WANTED for general English-speaking hospital. Applicant should be licensed and certified, or eligible to be certified in the Province of Quebec. Reply to Box 946, CMA Journal, 150 St. George St., Toronto 5, Ont.

POSITIONS VACANT.—July 1962 to July 1963. Positions in the general practice training program associated with the Ormstown Medical Centre and the Barrie Memorial Hospital, Ormstown, Quebec. Previous junior rotation required. For particulars apply to Dr. M. R. Stalker, Ormstown, Quebec.

PSYCHIATRIST WANTED for position in new mental health clinic to service three towns within a radius of forty miles on south shore of Nova Scotia. Office facilities, stenographic help, etc. provided. Duties to start in about six months' time. Salary guaranteed by provincial grants with excellent possibilities for private practice. Reply to Dr. James A. Wickwire, Liverpool, Nova Scotia.

REGISTERED and licensed practical nurses for integrated hospital. Top salary; excellent fringe benefits; opportunities for advancement. Contact: Administrator, Sidney Sumby Hospital, 234 Visger Road, River Rouge 18, Michigan, U.S.A.

TEACHING FELLOWSHIP in clinical pathology University of Alberta.—Applications are invited for the above teaching fellowship. Applicants must have a medical degree and at least two-year postgraduate training in pathology or medicine. Participation in teaching of undergraduate medical students, a research project, and in graduate training program in clinical pathology required. Stipend $3000 per annum. Applications should be addressed to Dr. R. E. Bell, Director, Department of Clinical Laboratory Services, University of Alberta Hospital, Edmonton, Alberta.

WANTED.—Assistant for busy general practitioner on Vancouver Island, B.C. Adequate 80-bed hospital being enlarged in growing district serving dependents of large R.C.A.F. Station. Pleasant area with good schools and moderate climate. Partnership considered if mutually suited. Apply to Box 114, CMA Journal, 150 St. George St., Toronto 5, Ont.

WANTED.—ASSISTANT with definite opportunity for partnership if desired with busy general practitioner in large Alberta city after January 1962. Salary commensurate with experience; car allowance included, alternate week-ends free. Please write stating age, experince, marital status and religion to Box 102, CMA Journal, 150 St. George St., Toronto 5, Ontario.

WANTED OTOLARYNGOLOGIST, certified for a well-known medical centre in Toronto. Good salary and opportunity for partnership. Reply to Box 585, CMA Journal, 150 St. George St., Toronto 5, Ont.

WANTED.—Well-qualified internist for small group in western Canadian city. Apply to Box 105, CMA Journal, 150 St. George St., Toronto 5, Ont.

Practices

NOTE: To avoid the publication of misleading information, all advertisers under the classification "Practices" in the Canadian Medical Association Journal should furnish the following information:

Population of community and surrounding territory served.

Number of doctors now practising in the community.

Location of nearest doctor if the community has no resident physician.

Location of nearest hospital.

Description and suggested price of premises for office and residence.

Whether or not an introduction of at least two months' duration may be afforded a prospective purchaser.

FOR SALE.—Well-established general practice in Vancouver. Furnishings and equipment like new. Average annual gross over $20,000. Present tenant considering leaving for personal reasons. Will sell reasonably on terms if desired. Direct inquiries to Residence, 1258 West 49th Ave., Vancouver or phone AM. 1-6488 evenings.

GENERAL PRACTICE FOR SALE.—Well-established in central Alberta, near Edmonton. Annual income gross: $25,000-$30,000. Most reasonable terms. Owner leaving for specialization. Apply to Box 60, CMA Journal, 150 St. George St., Toronto 5, Ont.

UNOPPOSED WELL-ESTABLISHED SURGICAL with general practice, lakeside central Manitoba. Well-equipped hospital. Dwelling and office combined, two lots, two garages. Good appointments. Annual income netting over $25,000. Will sell for value of property and equipment. Reasonable down payment and easy terms. Introduction given. Reply to Box 115, CMA Journal, 150 St. George St., Toronto 5, Ontario.

WANTED.—DOCTOR to take over practice at Glendon, Alberta. A 16-bed hospital serving a population of about 450. Arrangements could be made to take over practice at any time after December 7, 1961. Residence available for purchase or rent. Please contact Dr. J. C. Stephens, Glendon, Alberta. (phone 2) or L. F. Krawchuk, Secretary-Treasurer, Glendon, Alberta. (phone 2).

WELL-ESTABLISHED GENERAL PRACTICE in east Toronto; tremendous opportunity. Willing to sacrifice for little more than cost of equipment. No real estate involved. Can introduce. Apply to Box 107, CMA Journal, 150 St. George St., Toronto 5, Ont.

Residencies and Internships

APPROVED ROTATING INTERNSHIP AND GENERAL PRACTICE residencies available. Also unapproved residencies in medicine and surgery. Medical student externships open at all times. Write Dr. John E. Allen, Director of Medical Education, 12345 Cedar Road, Cleveland Heights 6, Ohio, U.S.A.

PATHOLOGY.—Fully-approved residencies, PA, CP. Two vacancies any level, three pathologists, microbiologist, biochemist. 8000 surgicals (475 frozens) 200 autopsies, 375,000 clinical tests, 300 general beds. Texas Medical Center (medical and postgraduate schools, library research). Laboratory fully-staffed and equipped. Active teaching and progressive responsibility. Participation in national meetings. American and Canadian graduates preferred. Satisfactory stipend. Personal interview, our expenses required. Reply to C. J. Lind, Jr., M.D., St. Luke's Episcopal Hospital, Houston 25, Texas.

PATHOLOGY RESIDENCY.—4-year approved program in pathologic anatomy and clinical pathology supervised by four pathologists, two biochemists and bacteriologist. 710-bed hospital, over 6000 surgicals and 400 autopsies. Opportunities for research in ultra-micro chemistry and new diagnostic methods; animal research facilities under construction. Apply: Edwin M. Knights, Jr., M.D., Pathology Department, Hurley Hospital, Flint 2, Michigan, U.S.A.

STATE OF CONNECTICUT, FAIRFIELD STATE HOSPITAL, NEWTOWN, CONN, U.S.A. Residents in Psychiatry.—Applications are invited for men and women graduates of Canadian medical schools for residency training in psychiatry. Large modern hospital with three-year training accreditation for American board certification. Active and varied teaching program in affiliation with Yale University. Close to metropolitan areas. Maintenance at nominal cost immediately available for single applicants, waiting list for family accommodations. Beginning stipend $455 per month. Write giving particulars to Jane E. Oltman, M.D., Director of Training.

WESTMINSTER HOSPITAL has the following positions available for intern staff from July 1, 1962 to June 30, 1963: Residents—$350; Assistant residents—$300 and senior interns—$260 per month. Vacancies are available in medicine, surgery, psychiatry, anesthesia, radiology, pathology and physical medicine. Westminster Hospital is conducted by the Department of Veterans Affairs and is a 1500-bed hospital with both psychiatry and general treatment patients. It is approved for training by the Royal College of Physicians and Surgeons of Canada and it is closely integrated with the teaching program of the University of Western Ontario Medical School. For further particulars apply to Chairman, Intern Committee, Westminster Hospital, London, Ontario.

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1. Meyers, G. B.: Ind. Med. & Surg. 26:3, 1957. 2. Murray, R. J.: N. Y. St. J. Med. 53:1867, 1953.

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Dec. 9, 1961, vol. 85

MEDICAL NEWS *in Brief*

(Continued from page 1312)

KENNAWAY AND THE CARCINOGENS

A recounting of the career of a pioneer in medicine should always deserve the close attention of medical readers. This is particularly true of a career such as that of Ernest Kennaway during which the foundations of much of modern knowledge of carcinogenesis were laid. The work of this patient and methodical scientist was the subject of the first Sir Ernest Kennaway Memorial Lecture delivered at the Chester Beatty Research Institute, Royal Cancer Institute, London, on June 12, 1961. The following abstract of the Lecture is reproduced by the kind permission of Professor Antoine of Paris and the editors of *Nature*.

"I first met Ernest Kennaway in 1923 at the Cancer Hospital in London when he was working on the isolation of the active carcinogenic principles in tar. In the following year Kennaway began to publish the results of the researches; the importance had escaped me a year earlier, yet the discovery of a 'carcinogenesis factor', by the pyrolysis of various organic substances, was to prove one of the most fertile in the whole of cancer research. It supplied the solution to a riddle which for more than 150 years had puzzled clinicians confronted with 'industrial cancers', but unable to understand how they arose. It opened the important chapter of chemical carcinogenesis which was to be written over the ensuing years by Kennaway himself (as director of the Research Institute of the Cancer Hospital and professor of experimental pathology) and the team of brilliant co-workers with whom he had surrounded himself. Through this work, organic chemistry was to be enriched by hundreds of new substances, and the way opened to the prophylaxis of industrial cancers.

"Great scientific discoveries come about by two means. Some are born of almost magical intuition and good fortune, suddenly laying bare a whole unsuspected realm of Nature. Others are reached by patient work and devoted attention to a particular problem. Kennaway's discovery was of the latter kind.

"The observation made at the end of the eighteenth century by the British surgeon, Percivall Pott, of a relationship between the development of certain cutaneous cancers and irritation of the skin by the combustion products of coal tar, had been followed by others. Experimental work on the suspected carcinogenicity of tar, pitch and paraffin was started at the end of the nineteenth century. Not until 1915, however, was a positive and conclusive result obtained, by the sensational discovery by Yamagiwa and Ichikawa. Work was at once started in various laboratories the world over to follow up their results. It was recognized that the mouse was the animal of choice, the most convincing results being obtained in this mammal in the shortest time. The lack of conformity in the results, however, led to the observation that the activity of tars varied according to their origin. Opinions differed as to which of the numerous constituents of coal tar might be responsible for its

(Continued on page 30)

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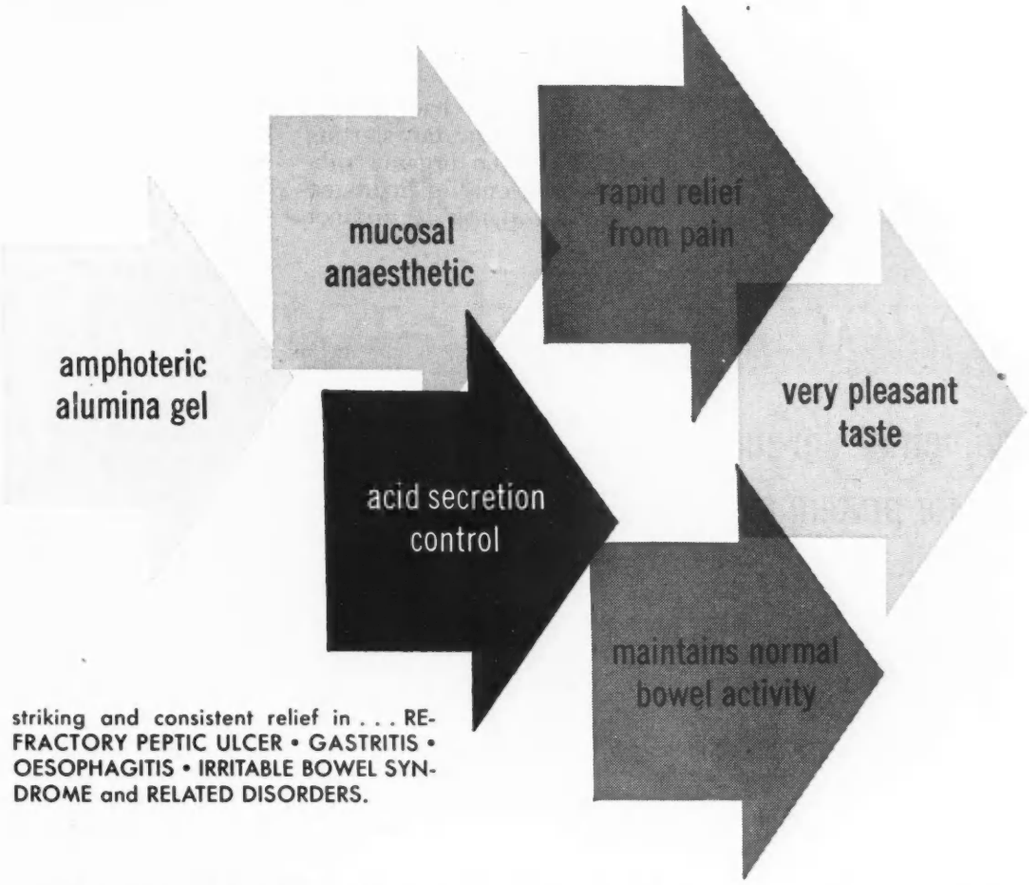

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MEDICAL NEWS *in brief*

(Continued from page 28)

carcinogenic activity, suspicion being directed against arsenic, the phenols, the pyrols, aniline, benzidine, anthracene and others. A first pointer came with the recognition that only the highest boiling fractions, distilling at temperatures above 300°, possess carcinogenic activity.

"It was to the unravelling of this tangled skein that Kennaway had set himself. His patient and methodical work was to supply a thread which, a few years later, was to lead the workers at the Cancer Hospital, through a rapid succession of discoveries, to write one of the fairest pages in the history of science.

"Having observed that compounds distilling at a very high temperature were for the most part hydrocarbons, he had the idea of making a synthetic tar, starting from a very simple organic substance consisting only of hydrogen and carbon. A pyrolysis product of isoprene was tested on the skin of a mouse, with a positive result, and Kennaway's well-reasoned hypothesis was confirmed. Actually, he obtained a higher proportion of tumours than with ordinary coal tars.

"In 1925, Kennaway confirmed the results which he had published the previous year, this time using acetylene. The activity of acetylene tars varied according to the temperature at which they were prepared. Other synthetic tars prepared from different organic substances, both animal and vegetable, also proved carcinogenic. In 1930, Kennaway published an even more important observation, starting this time from a tetrahydrogenated derivative of naphthalene, tetraline. Under the action of aluminium chloride this pure hydrocarbon acquires new properties, being in fact transformed into carcinogenic compounds. Since the work of Berthelot in 1864 it had been known that the pyrolysis of acetylene gives aromatic hydrocarbons by the cyclization of acyclic hydrocarbons. It therefore seemed probable that carcinogenic polycyclic hydrocarbons had in fact been produced in the earlier experiments also.

"In 1932, Cook, in collaboration with Hewett and Hieger, had succeeded in isolating from coal tar a pentacyclic hydrocarbon, 3,4-benzpyrene, which proved to be a much more potent carcinogen than the other previously synthesized. Eight years of methodical work had thus supplied a solution to the problem posed a century and a half earlier.

"3,4-benzpyrene seems to be the carcinogenic hydrocarbon produced most frequently and most abundantly in soot from coal fires, in the treatment of mineral oils, and, in certain circumstances, from the combustion of petroleum – all substances derived from the luxuriant vegetable and animal matter laid down during the primary era. 3,4-benzpyrene is also the principal hydrocarbon in cigarette smoke and in the vitiated air of industrial cities. It will be seen that the discoveries, of which Kennaway was the author or initiator, exercise a continuing repercussion on public life to-day.

"Since the induction of tumours by chemical means had now been amply demonstrated, it seemed

(Continued on page 32)

MEDICAL NEWS *in brief*
(Continued from page 30)

that an understanding of the mechanism of carcinogenesis should soon lie within our reach. The relationship between the molecular structure and carcinogenic activity of chemical compounds was clear. The skeleton of the majority of them contains the phenanthrene ring system; oncogenic activity can be produced, enhanced, weakened or destroyed by simple substitutions on the molecule. It became possible to judge the carcinogenic potency of a given molecule simply from the ring configuration and the position of the substituents.

"The similarity between the skeletons of the carcinogenic hydrocarbons and that of equilenin (a sex hormone discovered by Girard in 1932 in the urine of pregnant mares) did not escape the attention of the research workers in Great Britain. Was it not therefore conceivable that certain normal metabolites, of steroid structure, might be transformed into carcinogenic compounds in the body itself, as a result of one or more errors of metabolism? It was in fact not long before a new aromatic hydrocarbon, 3-methylcholanthrene, was obtained and found to be even more active than 3,4-benzpyrene; it was produced synthetically from a bile acid, deoxycholic acid, by dehydrogenation processes of which the organism is, however, known to be capable.

"The rapid progress in theoretical chemistry, aided by the powerful electronic computers, has consolidated the quantum theory of chemical carcinogenesis to the point where it is possible to predict the carcinogenic activity of hydrocarbons before they have been tested. Investigations of the electron densities in the molecule of 3,4:9,10-dibenzpyrene suggested that this substance might be highly carcinogenic. Its synthesis and subsequent testing on the mouse proved it to be one of the most potent carcinogens known. The close relationship between this biological property and the molecular constitution of the compound indicates that there is a direct causal connexion between them, as Kennaway had assumed.

"Again, quite recently, we have confirmed another of Kennaway's important theses and found that the induction of certain spontaneous tumours may be due to certain metabolic variations in the biogenesis or the catabolism of natural steroids.

"In spite of this brilliant work, one is obliged to admit that the accumulated research of half a century into the pathogenesis of tumours has still only brought us to the beginning of an understanding of the problem. Nevertheless, one can safely say that the results obtained from the study of chemical carcinogenesis still seem to stand out above all else in this difficult field—even in this era of virus research. They bear witness to Kennaway's worth and to the immortality of his work. His discoveries supplied the scientific bases necessary for the solution of many problems of occupational, preventive and social medicine to which this generous and forward-thinking man dedicated himself during the last years of his life."

(Continued on page 34)

MEDICAL NEWS *in brief*
(Continued from page 32)

IDENTIFICATION OF POLIOVIRUS ISOLATES WITH FLUORESCENT ANTIBODY

A specific and relatively rapid direct fluorescent antibody staining method for laboratory identification of polioviruses isolated from stool samples is reported by Hatch, Kalter and Ajello (*Proc. Soc. Exper. Biol.*, 107: 1, 1961). Eighty-five stool specimens were processed as unknown in a comparison between the routine method employing neutralization tests and the fluorescent antibody method. Thirty-eight were found to contain Poliovirus types 1, 2 or 3 by the regular procedure, and 34 of these were correctly identified by the fluorescent antibody method. The other four of the 38 were negative by fluorescent antibody. The 47 specimens found not to contain poliovirus by the routine method were negative by fluorescent antibody. Eighteen of these contained other enteroviruses. Thus, although the fluorescent antibody procedure was found slightly less sensitive than the routine procedure, it was entirely specific in this study.

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MEASUREMENT OF THE PROTECTIVE EFFECT OF ATTENUATED POLIOVIRUS VACCINE

In an attempt to solve the problem of measuring the effectiveness of live poliovirus vaccine in preventing paralytic disease, Knowelden *et al.* (*Brit. M. J.*, 1: 1418, 1961) recorded the following data during the type I epidemic in Singapore in late 1958 and early 1959. These have been analysed. Sabin type II vaccine was fed to about 200,000 of the half-million children under 10 years of age, beginning in the twelfth week of the epidemic. For each subsequent week estimates were made of the child populations in three categories: unvaccinated, vaccinated less than eight days, and vaccinated eight or more days previously. It is shown that the number of patients (8) who developed paralytic poliomyelitis less than eight days after vaccination was close to that expected at the rates in unvaccinated children (10.2), whereas the five cases observed in children vaccinated a longer period before onset were many fewer than the expected number of 39.46. It is concluded that a week after feeding the Sabin type II strain a substantial reduction in the risk of paralytic disease occurred as a result of vaccination.

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X-RAY LIMITATIONS

New York State's Health Department has taken steps to enforce a ban on use of x-ray equipment by chiropractors, according to the *A.M.A. News* (August 21, 1961). The State's Public Health Council in 1957 added a provision to New York's Sanitary Code which forbade chiropractors to use x-ray radiation, but the ban was delayed three years by a court test of the provision. The court action was dismissed last May.

(Continued on page 36)

MORE EFFECTIVE CONTROL

"Chlorpropamide produced . . . excellent control in more than twice as great a percentage than did tolbutamide."

S. K. Fineberg, Journal of the American Geriatrics Society, Vol. VIII, No. 6, June 1960.

"Chlorpropamide is more potent than tolbutamide in blood-sugar lowering ability."

J. N. Sugar, et al., A.M.A. Archives of Internal Medicine, Sept. 1959, Vol. 104

"On the above evidence chlorpropamide is the more effective sulphonylurea at present available."

D. Jackson and W. Oakley, Lancet *11:* 752, Nov. 1959.

OF MORE DIABETICS

"Of patients who lost responsiveness to tolbutamide, 62% were satisfactorily managed with chlorpropamide."

Samuel J. N. Sugar, et al., A.M.A. Archives of Internal Medicine, Sept. 1959, Vol. 104.

"At the dose levels stated (200-500 mg. daily) chlorpropamide has a wider range of action than tolbutamide . . ."

Granville - Grossman, K. L.; Crawford, S.; Crowley, M.F., and Bloom, A.: Brit. M.J. *2:* 841, 1959.

MORE ECONOMICALLY

"Tolbutamide for one month costs $11.25 buying 'brand names', chlorpropamide $7.20 . . ."

William T. W., Clarke, Mod. Med. of Can., page 70, Nov. 1960.

WITH DIABINESE

CHLORPROPAMIDE

ONCE A DAY DOSAGE

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Scored Tablets: 250 mg. bottles of 30 and 100.
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1961P

MEDICAL NEWS *in brief*

(Continued from page 34)

REFRESHER COURSE IN EYE SURGERY

The Faculty of Medicine, University of Toronto, will hold a Refresher Course in Eye Surgery, April 9-11, 1962. The instruction will consist of lectures, operative sessions and a special symposium on glaucoma surgery.

Dr. Arthur Gerard DeVoe, Institute of Ophthalmology, New York, and Mr. P. D. Trevor-Roper, Westminster Hospital, London, England, will be guest surgeons. The staff of the Department of Ophthalmology will contribute extensively.

The course will be limited to 50 members and is open to eye, ear, nose and throat specialists. Application should be made to the Director, Division of Postgraduate Medical Education, Faculty of Medicine, University of Toronto, Toronto 5, Ontario, before March 9, 1962.

On April 7 there will be a Departmental Research Meeting and Dr. Endre A. Balazs, The Retina Foundation, Boston, will be guest speaker. Members of the Eye Surgery Course are cordially invited to attend.

—

NATURE OF THE GENE

Demerec (*Am. J. Hum. Genet.*, 13: 122, 1961) points out that a gene locus comprises a finite section of a chromosome (or *genestring*) and contains the information necessary to control a particular chemical reaction or class of reactions. Within the gene locus in micro-organisms, smaller units (sites) can be identified by means of recombination experiments. A site represents the smallest portion of genetic material that is not divisible by recombination. A change (mutation) occurring at any one of its many sites affects the expression of a whole gene locus.

Mutants resulting from mutations at different sites of the same gene locus, or even at the same site, may differ from one another in several respects (stability, reaction to mutagens, temperature sensitivity, nutritional requirements, complementary relations). As a rule, however, such mutants have one feature in common: they are changed with regard to a specific function, controlled by that particular gene locus. In some or perhaps most cases, control of the function is effected through an enzyme whose structure, and consequently in a large measure character and specificity, are determined by the gene.

The findings about the structure of loci are in accordance with the view that DNA is the carrier of genetic information in phages and bacteria, and with the model of DNA structure proposed by Watson and Crick (1953). Observations concerning the nature of sites can be accounted for by assuming that a site is represented in the DNA molecule by either one or a few nucleotide pairs. Recently it has been estimated by Hershey that phage T2 has one or two DNA molecules and about 20-30 genes. Thus a considerable number of gene loci are contained in one molecule.

Demerec stresses that the ideas discussed have developed as logical steps in a chain of discoveries

begun almost half a century ago. Attention is directed to various scientists who participated in these discoveries.

—

EFFECT ON THE FETUS OF VIRAL DISEASE IN THE MOTHER

In most of the common infectious diseases due to viruses, evidence exists that the virus can be transmitted to the fetus through the placenta. Why this does not occur more often is not known.

According to Potter (*Clin. Obst.*, 4: 327, 1961), viruses vary in their effect on the fetus. Rubella exerts its effect only in the early weeks of pregnancy, when it may be responsible for changes in growth patterns leading to malformations. No other virus is known to have a similar effect, although poliomyelitis may possibly be responsible for abortion.

Many viruses may lead to disease similar to that in the mother when disease occurs late in pregnancy: especially in the case of variola, varicella and rubeola, and possibly influenza, parotitis, herpes zoster and western equine encephalomyelitis.

Certain viruses lead to severe, generalized, often fatal disease of an entirely different form from that observed in the mother. These are especially herpes simplex, Coxsackie Group B virus, and salivary-gland virus.

—

POSSIBLE TERATOGENIC EFFECT OF TOLBUTAMIDE IN PREGNANCY

It is reported that in the diabetic clinic of the King Edward VIII Hospital in Durban, the sulfonylureas are being given routinely to about 90% of the pregnant Natal Indian diabetics, and to control patients who develop glycosuria in pregnancy.

It is pointed out by Campbell (*Lancet*, 1: 891, 1961) that these pregnant diabetics represent a recently described tropical variant of diabetes referred to as the "insulin-independent young diabetics"; they do not depend on exogenous insulin in the ordinary course of events, even though they present with the classical symptoms of diabetes (but they never become ketotic). It is stated these patients make up 16% of the Natal Indian diabetics, and they are most commonly in their early twenties at the onset of diabetes.

A report of 21 such insulin-independent young pregnant diabetics taken through pregnancy (excluding pregnancy glycosurics) is given with a fetal loss of 5, including one grossly congenitally malformed. The poor obstetric history of this particular mother is noted, and the author states it is interesting that in this small series it was only in this patient with the worst history that teratogenesis was found.

In a small series of these pregnant patients it has been found that the sulfonylureas can supplant insulin in over 90%. In view of the importance, for those intending to give these drugs, of knowing whether they can cause fetal malformations, the author urges that any further cases be promptly reported.

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MEDICAL NEWS *in brief*

(Continued from page 37)

PURIFIED POLIOVACCINE

Six years' experience has clearly established the effectiveness of killed poliovaccines against paralytic disease, and levels of protection ranging from 65 to 95% have been reported from different countries, in which the local circumstances have varied considerably.

An editorial in the *British Medical Journal* (1: 1522, 1961) states that the prime importance of the quantity of viral antigen in the vaccine has been stressed by Salk and many others. It is also noted that poliovaccines prepared in monkey-kidney tissue cannot be concentrated by a single procedure such as centrifugation, owing to the small size of the virus particle. Accordingly, it is stated, the potency of the vaccine depends very largely on the initial titre of the virus fluids before inactivation and the amount of type I component included.

Attention is directed to a paper by Hilleman and his colleagues (*Excerpta Medica International Congress Series*, No. 27: 16, 1961) reporting progress in the development of a purified and concentrated poliovaccine by a chemical process in which the amount of antigen for each of the three virus types has been standardized. It is stated that two doses of vaccine produced an excellent antibody response in 90% of those vaccinated. It is pointed out that the main advantage of this purified product is that the strength of the vaccine can be readily increased by incorporating the correct amount of concentrate.

Two other advantages are noted: first, the use of concentrated polio antigen is necessary for the immunization of infants with a quadruple vaccine if the effect of maternal antibody is to be overcome; and secondly, the removal of detectable monkey-kidney antigen by the purification process may reduce the risk of reactions, such as the rare cases of acute neurological disturbance discussed by Spillane at a meeting of the Section of Neurology, Royal Society of Medicine, May 1961.

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MUSCULOSKELETAL MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

The onset of systemic lupus erythematosus (SLE) is often marked by seemingly innocent musculoskeletal symptoms, and these may dominate its early course. Unless they are recognized, patients may go on for a long time with some rheumatic diagnosis until an acute febrile episode or visceral or cutaneous symptoms afford clues to the correct diagnosis. In the course of seven years, 23 cases of SLE have been found among the patients attending the rheumatology service of a hospital for joint diseases; these are described by Silver and Steinbrocker (*J. A. M. A.*, 176: 1001, 1961). The musculoskeletal symptoms varied from patient to patient and from time to time, and resembled a variety of other rheumatic states. Two imporant diagnostic clues are the frequent remissions and exacerbations with few or no residuals and the discrepancy between severe rheumatic symptoms and inconspicuous physical and roentgenographic changes.

(Continued on page 40)

When the patient is plagued with the aches and pains of "la grippe"...

NEW PERIACTIN-APC*

TABLETS

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For Prompt Symptomatic Relief

Histamine and serotonin have been implicated in coryza, rhinitis and headache, therefore PERIACTIN* (Cyproheptadine Hydrochloride), a potent antagonist of histamine and serotonin, has been combined with the classic therapeutic triad of Acetylsalicylic Acid, Phenacetin and Caffeine, to provide a multiple attack upon — the miseries and symptoms of "la grippe" and the "common cold".

With this association of several components specific in their action against individual symptoms, PERIACTIN-APC* can be of real value to the patient with the multiple complaints of "la grippe" or the "common cold". He may derive relief from malaise, fever, headache, sinusitis, laryngitis, pharyngitis, myalgia, coryza, rhinorrhea and conjunctivitis, which are among the symptoms amenable to palliation and control with PERIACTIN-APC.

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MEDICAL NEWS *in brief*

(Continued from page 38)

WORLD FEDERATION OF NEUROSURGICAL SOCIETIES

At a meeting of the Executive Committee of the World Federation of Neurosurgical Societies held in Washington, D.C., during the Second International Congress of Neurological Surgery, October 14-20, 1961, the following officers were elected: President, Prof. Eduard Busch, Copenhagen, Denmark; Vice-President, Dr. Kentaro Shimizu, Tokyo, Japan; Secretary for the World Federation of Neurosurgical Societies, Dr. A. Earl Walker, Baltimore, Md., U.S.A.; Secretary for the Third International Congress of Neurological Surgery, Mr. D. W. C. Northfield, London, England; Assistant Secretary for the Third International Congress of Neurological Surgery, Dr. Bendt Broager, Copenhagen, Denmark; Treasurer, Dr. H. Krayenbühl, Zürich, Switzerland; Assistant Treasurer, Dr. Richard Malmros, Aarhus, Denmark; Editor of Publications, Dr. A. C. de Vet, The Hague, Netherlands.

The Third International Congress of Neurological Surgery will be held in Copenhagen, Denmark, in 1965. The dates will be announced later.

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NICARAGUA, PERU AND URUGUAY ELECTED TO PAHO EXECUTIVE COMMITTEE

Nicaragua, Peru and Uruguay were recently elected to the Executive Committee of the Pan American Health Organization. The newly elected nations replace Brazil, Honduras and the United States, whose three-year terms on the Committee have expired.

The Executive Committee is made up of the representatives of seven American nations who meet twice a year on behalf of all the American Republics. Other nations now serving are Argentina, Chile, Colombia, and El Salvador.

PAHO's Directing Council is made up of the representatives of the 21 American Republics, plus those of France, the Netherlands and the United Kingdom on behalf of their territories in the Americas.